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# Antagonists of Slow-Reacting Substance of Anaphylaxis. 1. Pyrido[2,1-*b*]quinazolinecarboxylic Acid Derivatives

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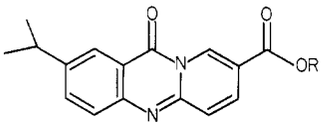
Members of a series of basic amide and ester derivatives of 2-substituted pyrido[2,1-*b*]quinazoline-8-carboxylic acids were prepared and evaluated for their ability to prevent slow-reacting substance of anaphylaxis (SRS-A) induced contractions of guinea pig ilea. The results indicate that the presence of a branched-chain alkyl group in the 2-position and a sterically demanding substituted aminoethyl carboxylate or carboxamide in the 8-position give optimal in vitro activity. The phenylpiperazine **25** was further found to block SRS-A-related symptomatology after intravenous administration in two animal models.

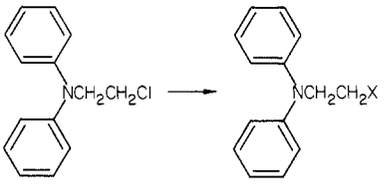
We[1] and others[2,3] have recently described a series of pyrido[2,1-*b*]quinazolinecarboxylic acids which constitute a new class of orally active antiallergy agents. Representative compounds from this series have been characterized in our laboratories as mediator release inhibitors with a mechanism of action similar to that of disodium cromoglycate.[4,5] One of the most interesting orally active compounds to emerge from this work was the 2-isopropyl derivative **1**. Surprisingly, the corresponding (diethylamino)ethyl ester **2** proved to prevent the constrictions elicited in the guinea pig ileum by slow-reacting substance of anaphylaxis (SRS-A), although its parent acid **1** was inactive. This finding led to the preparation and evaluation of structures related to **2**, which are documented in this paper. Aspects of the structure–activity relationships for in vitro activity in the guinea pig ileum in the pyridoquinazoline series have been defined, and the activity of the phenylpiperazine **25** has been further demonstrated in two in vivo models that mimic SRS-A-related symptomatology.



**1**, R = H
**2**, R = $(CH_2)_2N(C_2H_5)_2$

**Chemistry.** The analogues of **2** listed in Tables I–III were prepared from the corresponding pyrido[2,1-*b*]-quinazolinecarboxylic acids. The esters described in Table I were synthesized by reaction of the appropriate carboxylic acid with (diethylamino)ethyl chloride (method A) or by reaction of the acid chloride with an amino alcohol (method B). The amyl ester **9** was obtained by ester exchange of **2** in refluxing amyl alcohol (method C).

The amides listed in Table II resulted from coupling of pyrido[2,1-*b*]quinazolinecarboxylic acids with the appropriate amines either via the acid chlorides (method D) or, somewhat more efficiently, utilizing diphenylphosphoryl azide (method E).[6] *N,N*-Diphenylethylenediamine (**29**) was synthesized from 2-(diphenylamino)ethyl chloride[7] through reaction with potassium phthalimide in DMF to give the phthalimide **28**, which was cleaved with hydrazine.



**28**, X = phthalimide
**29**, X = $NH_2$

The new pyrido[2,1-*b*]quinzoline-8-carboxylic acids (Table IV) were obtained from condensation of 6-chloronicotinic acid with a 5-substituted anthranilic acid in either triglyme containing a catalytic amount of potassium iodide (method F) or in ethylene glycol methyl ether made 1% in formic acid (method G). The 5-substituted anthranilic acids required for **32** and **33** were obtained[8] via aromatic nucleophilic displacement reactions starting with 5-chloro-2-nitrobenzoic acid. The precursor 5-alkylanthranilic acids for **34** and **35**[9] were made available through an unusally facile palladium-catalyzed carbonylation of the corresponding 4-alkyl-2-bromoacetanilides, and 5-*tert*-butylanthranilic acid, the starting material for **36**, was synthesized by the isatin route.[10]

## Discussion

The compounds listed in Tables I–IV were evaluated for their ability to prevent constrictions induced by SRS-A in vitro by utilizing the guinea pig ileum bioassay technique described by Orange and Austen.[11] Isotonic contractions of guinea pig ileum segments suspended in an oxygenated buffer solution containing $1 \times 10^{-6}$ M atropine sulfate and $1 \times 10^{-6}$ M pyrilamine maleate were elicited with SRS-A obtained by antigen challenge of actively sensitized, chopped guinea pig lung fragments. A dose of SRS-A that gave 50% of the maximal contraction was used. The compounds were tested in duplicate at three concentrations that caused inhibitory effects of between 10 and 90%. The $IC_{50}$ values given in the last column of tables were calculated from the log dose–response curves. Those

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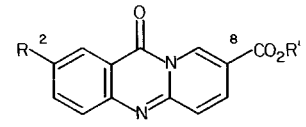
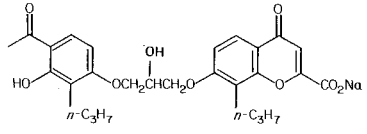
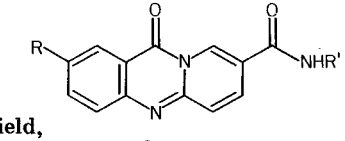
**Table I. Anti-SRS-A Activity of Pyrido[2,1-*b*]quinazolinecarboxylates**

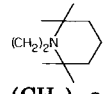


| compd | R | R′ | method | yield, % | mp, °C | solvent | formula | anal. | anti-SRS-A act.: $IC_{50}$,[a] M |
|---|---|---|---|---|---|---|---|---|---|
| 2 | $i$-$C_3H_7$ | $(CH_2)_2N(Et)_2$ | A | 96 | 221-222 | $CH_2Cl_2$-$Et_2O$ | $C_{22}H_{27}N_3O_3$·HCl | C, H, N, Cl | $4 \times 10^{-6}$ |
| 3 | O-$i$-Pr | $(CH_2)_2N(Et)_2$ | A | 58 | 208-209 | MeOH | $C_{22}H_{27}N_3O_4$·HCl | C, H, N, Cl | inact (17) |
| 4 | $OCH_3$ | $(CH_2)_2N(Et)_2$ | A | 56 | 255-258 | MeOH-$Et_2O$ | $C_{20}H_{23}N_3O_4$·HCl | C, H, N, Cl | inact (0) |
| 5 | $SCH_3$ | $(CH_2)_2N(Et)_2$ | A | 92 | 236-238 | MeOH | $C_{20}H_{23}N_3O_3S$·HCl | C, H, N, Cl, S | inact (0) |
| 6 | $CH_3$ | $(CH_2)_2N(Et)_2$ | B | 73 | 236-238 | EtOH-$Et_2O$ | $C_{20}H_{23}N_3O_3$·HCl | C, H, N, Cl | inact (11) |
| 7 | $i$-$C_3H_7$ | $(CH_2)_2$-c-$NC_5H_{10}$ | B | 12 | 242-243 | MeOH-$CH_2Cl_2$-Hex | $C_{23}H_{27}N_3O_3$·2HCl·0.25$H_2O$ | C, H, N, Cl | $6 \times 10^{-6}$ |
| 8 | $i$-$C_3H_7$ | $CH(CH_3)CH_2N(Et)_2$ | B | 8 | 203-204 | $CH_2Cl_2$-Hex | $C_{23}H_{29}N_3O_3$·1.7HCl | C, H, N, Cl | $1 \times 10^{-5}$ |
| 9 | $i$-$C_3H_7$ | $(CH_2)_4CH_3$ | C | 69 | 107-108 | Hex | $C_{21}H_{24}N_2O_3$ | C, H, N | inact (10) |
| 10 |  | | | | (FPL 55712) | | | | $3.5 \times 10^{-8}$ |

[a] Molar concentration of drug giving 50% inhibition of SRS-A-induced contraction of guinea pig ileum strips. Numbers in parentheses are the percent inhibitions observed at $1 \times 10^{-5}$ M.

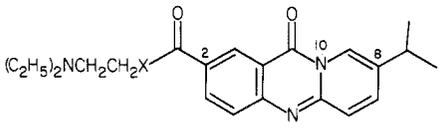
**Table II. Anti-SRS-A Activity of 2-Substituted Pyrido[2,1-*b*]quinazoline-7-carboxamides**



| compd | R | R′ | method | yield, % | mp, °C | solvent | formula | anal. | anti-SRS-A act.: $IC_{50}$,[a] M |
|---|---|---|---|---|---|---|---|---|---|
| 11 | $i$-$C_3H_7$ | $(CH_2)_2N(C_2H_5)_2$ | D | 45 | 256-258 | MeOH-$Et_2O$ | $C_{22}H_{28}N_4O_2$·2HCl·$^1/_3H_2O$ | C, H, N, Cl | $5 \times 10^{-6}$ |
| 12 | $s$-$C_4H_9$ | $(CH_2)_2N(C_2H_5)_2$ | D | 22 | 245-248 | EtOH-$Et_2O$ | $C_{23}H_{30}N_4O_2$·2HCl·$^1/_2H_2O$ | C, H, N, Cl | $1 \times 10^{-5}$ |
| 13 | $i$-$C_4H_9$ | $(CH_2)_2N(C_2H_5)_2$ | D | 21 | 263-266 | EtOH | $C_{23}H_{30}N_4O_2$·2HCl | C, H, N, Cl | $1 \times 10^{-6}$ |
| 14 | $t$-$C_4H_9$ | $(CH_2)_2N(C_2H_5)_2$ | D | 41 | 256-258 | MeOH-$Et_2O$ | $C_{23}H_{30}N_4O_2$·2HCl [b] | C, H, N, Cl | $1 \times 10^{-5}$ |
| 15 | $i$-$C_3H_7$ | $(CH_2)_2N(CH_3)_2$ | D | 30 | 274-276 | MeOH-$Et_2O$ | $C_{20}H_{24}N_4O_2$·2HCl | C, H, N, Cl | inact (42) |
| 16 | $i$-$C_3H_7$ | $(CH_2)_2N(i\text{-}C_3H_7)_2$ | D | 74 | 247-250 | EtOH | $C_{24}H_{32}N_4O_2$·2HCl | C, H, N, Cl | $1 \times 10^{-6}$ |
| 17 | $i$-$C_3H_7$ | $(CH_2)_2N(c\text{-}C_6H_{11})_2$ | E | 67 | 205-207 | EtOH | $C_{30}H_{40}N_4O_2$·2HCl | C, H, N, Cl | $2 \times 10^{-6}$ |
| 18 | $i$-$C_3H_7$ | $(CH_2)_2N(C_6H_5)_2$ | E | 66 | 175-176 | $CH_2Cl_2$-Hex | $C_{30}H_{28}N_4O_2$ [c] | C, H, N | $1 \times 10^{-5}$ |
| 19 | $i$-$C_3H_7$ | $(CH_2)_3N(C_2H_5)_2$ | D | 63 | 175 | MeOH-$Et_2O$ | $C_{23}H_{30}N_4O_2$·2HCl | C, H, N, Cl | inact (37) |
| 20 | $i$-$C_3H_7$ | $(CH_2)_2$-c-$NC_5H_{10}$ | D | 24 | 276-277 | MeOH-$Et_2O$ | $C_{23}H_{28}N_4O_2$·2HCl | C, H, N, Cl | inact (15) |
| 21 | $i$-$C_3H_7$ |  | E | 79 | 261-262 | EtOH-$Et_2O$ | $C_{27}H_{36}N_4O_2$·2HCl | C, H, N, Cl | $1 \times 10^{-6}$ |
| 22 | $i$-$C_3H_7$ | $(CH_2)_2$-c-$NC_5H_{10}$-$C_6H_5$ | E | 35 | 270-275 | EtOH | $C_{29}H_{32}N_4O_2$·2HCl | C, H, N, Cl | $1 \times 10^{-6}$ |
| 23 | $i$-$C_3H_7$ | $(CH_2)_2$-c-$NC_5H_{10}$-$CH_2$-$C_6H_5$ | E | 40 | 273-275 | EtOH | $C_{30}H_{34}N_4O_2$·2HCl | C, H, N, Cl | $1 \times 10^{-6}$ |
| 24 | $i$-$C_3H_7$ | $(CH_2)_2$-c-$N(CH_2CH_2)_2N$-$CH_3$ | D | 78 | 203-205 | EtOH | $C_{23}H_{29}N_5O_2$·3HCl·$H_2O$ | C, H, N, Cl | inact (34) |
| 25 | $i$-$C_3H_7$ | $(CH_2)_2$-c-$N(CH_2CH_2)_2N$-$C_6H_5$ | E | 72 | 246-247 | EtOH | $C_{28}H_{31}N_5O_2$·HCl·$^1/_2H_2O$ | C, H, N, Cl, $H_2O$ | $1 \times 10^{-6}$ |
| 26 | $i$-$C_3H_7$ | $(CH_2)_2$-c-$N(CH_2CH_2)_2N$-$CH(C_6H_5)_2$ | D | 51 | 258-261 | EtOH | $C_{35}H_{37}N_5O_2$·3HCl | C, H, N, Cl | $1 \times 10^{-6}$ |
| 27 | $i$-$C_3H_7$ | $(CH_2)_2NH$-$C_6H_5$ | E | 57 | 274-275 | MeOH-$Et_2O$ | $C_{24}H_{24}N_4O_2$·HCl | C, H, N, Cl | $2.5 \times 10^{-6}$ |

[a] Molar concentration of drug giving a 50% inhibition of SRS-A-induced contraction of guinea pig ileum strips. Numbers in parentheses are the percent inhibition observed at $1 \times 10^{-5}$ M. [b] Cl: calcd, 15.17; found, 14.66. [c] Contains a trace (0.06 mol) of dichloromethane.

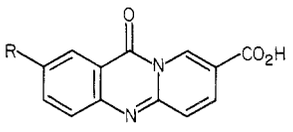
Table III. 8-(1-Methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-2-carboxylic Acid Derivatives



| compd | X | method | yield, % | mp, °C | solvent | formula | anal. | anti-SRS-A act.: $IC_{50}$,[a] M |
|---|---|---|---|---|---|---|---|---|
| 30 | O | A | 42 | 235–235.5 | *i*-PrOH | $C_{22}H_{27}N_3O_3 \cdot HCl$ | C, H, N, Cl | inact (5) |
| 31 | NH | D | 37 | 265–269 | MeOH-$Et_2O$ | $C_{22}H_{28}N_4O_2 \cdot 2HCl$ | C, H, N, Cl | inact (6) |

[a] Molar concentration of drug giving a 50% inhibition of SRS-A-induced contraction of guinea pig ileum strips. Numbers in parentheses are the percent inhibition observed at $1 \times 10^{-5}$ M.

Table IV. 2-Substituted Pyrido[2,1-*b*]quinazoline-8-carboxylic Acids



| compd | R | method | yield, % | mp, °C | solvent[a] | anal. | formula |
|---|---|---|---|---|---|---|---|
| 32 | O-*i*-$C_3H_7$ | F | 32 | 278–279 | *i*-PrOH-DMEA | C, H, N | $C_{16}H_{14}N_2O_4$ |
| 33 | $SCH_3$ | F | 15 | >310 | *i*-PrOH-DMEA | C, H, N, S | $C_{14}H_{10}N_2O_3S$ |
| 34 | *i*-$C_4H_9$ | G | 21 | 297–299 | DMF-HOAc | C, H, N | $C_{17}H_{16}N_2O_3$ |
| 35 | *s*-$C_4H_9$ | G | 23 | 296–298 | DMF-HOAc | C, H, N | $C_{17}H_{16}N_2O_3$ |
| 36 | *t*-$C_4H_9$ | F | 26 | 299–300 | DMF-HOAc-$H_2O$ | C, H, N | $C_{17}H_{16}N_2O_3$[b] |

[a] DMEA = 2-(dimethylamino)ethanol. [b] H: calcd, 5.44; found, 5.96.

compounds with $IC_{50}$s of greater than $1 \times 10^{-5}$ M were regarded as inactive, although the present inhibitions obtained at $10^{-5}$ M are also indicated in the last column of these tables. The parent acids listed in Table IV were inactive at $10^{-5}$ M as SRS-A antagonists in this test system.

Among a series of 2-(diethylamino)ethyl 2-substituted pyrido[2,1-*b*]quinazoline-8-carboxylates (Table I), only the isopropyl derivative **2** was active. Even such close analogues as the 2-methyl compound **6** were inactive, suggesting a requirement for a branched-chain alkyl moiety in the 2-position. The decreased activity of the amyl ester **9** indicates the importance of the amino nitrogen of **2**.

The hydrolytic instability of (diethylamino)ethyl esters makes them unsuitable for development as oral medications, and, thus, we were interested in determining whether the corresponding amides would also be active. The *N*-(diethylamino)ethyl amide **11** (Table II) had approximately the same potency as the corresponding ester **2**. In a series of *N*-(diethylamino)ethyl amides in which the nature of the branched-chain alkyl moiety in the 2-position was varied, the isobutyl analogue **13** was substantially more potent than the isopropyl compound **11**, while the *sec*-butyl (**12**) and *tert*-butyl (**14**) analogues were only minimally active.

In the amide series (Table II), we also sought to determine the effects on activity of variations in the *N*-(alkylamino)alkyl moiety. Increasing the distance between the basic nitrogen and amide nitrogen atoms from two to three carbons (**19**) led to a decrease in activity. Increasing the size of the alkyl group of *N*-(dialkylamino)ethyl amides from methyl (**15**) to ethyl (**11**) to isopropyl (**16**) or cyclohexyl (**17**) led to a progressive increase in activity. A similar apparent dependence of activity on steric effects was observed in a group of *N*-piperidinylethyl (**20–23**) and *N*-piperazinylethyl (**24–26**) analogues. The simple *N*-piperidinylethyl compound **20** and the 4-methyl-1-piperazinylethyl amide **24** were inactive, whereas the 2,2,6,6-tetramethylpiperidine **21**, as well as the 4-aryl and 4-arylalkyl derivatives **22–26**, had $IC_{50}$ values of $1 \times 10^{-6}$ M.

Neither of the compounds in Table III, in which the position of the isopropyl and carboxyl substituents were reversed, was active in vitro. This finding suggests that the location of the nitrogen atom in the 10-position of the pyridoquinazoline nucleus is critical in determining activity, in contrast to the results obtained in the rat passive cutaneous anaphylaxis test, in which it was observed that both the isopropyl acid **1** and the analogue with the substituents reversed were highly active.[1]

To summarize, the structural requirements for prevention of SRS-A-induced contractile activity in the pyrido-[2,1-*b*]quinazoline series include a branched-chain alkyl group, preferably isopropyl or isobutyl, in the 2-position and a sterically demanding substituted aminoethyl carboxylate or carboxamide in the 8-position.

The availability of a synthetic SRS-A, leukotriene $E_4$ ($LTE_4$),[12] has permitted us to develop two specific animal models to evaluate compounds for their ability to block SRS-A-related symptomatology in vivo.[13] In the first model, the inhibitory activity of the drug toward $LTE_4$-induced bronchoconstriction in guinea pigs was assessed. Animals pretreated with propanolol were given a dose of 10 mg/kg (iv) of test drug 30 s prior to challenge with a maximally constricting dose of $LTE_4$, and the percent inhibition of bronchoconstriction in comparison to control animals was measured. Those compounds described in Tables I–III that were active in vitro at $1–2 \times 10^{-6}$ M were evaluated in this model. The phenylpiperazine **25** gave an inhibition of 70 ± 7%, whereas the standard SRS-A antagonist, **10** (sodium 7-[3-(4-acetyl-3-hydroxy-2-propylphenoxy)-2-hydroxypropoxy]-4-oxo-8-propyl-4*H*-1-benzopyran-2-carboxylic acid, FPL 77512),[14] was more active, yielding a 98 ± 1% inhibition. The other com-

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(13) Welton, A. F.; Crowley, H. J.; Miller, D. A.; Yaremko, B. *Prostaglandins* **1981**, *21*, 287.
(14) Augustein, J.; Farmer, J. B.; Lee, T. B.; Sheard, P.; Tattersall, M. L. *Nature (London), New Biol.* **1973**, *245*, 215.

pounds reported herein were inactive.

The phenylpiperazine **25** was further tested in a second model in which the ability of $LTE_4$ to increase vascular permeability in rat skin was utilized. Rats, pretreated with an antihistamine, pyrilamine maleate, and a serotonin antagonist, methylsergide maleate, were injected intradermally with a standard dose of $LTE_4$ and intravenously with Evans blue dye, resulting in the formation of a skin wheal. Injection of 10 mg/kg (iv) of **25** immediately after $LTE_4$ challenge resulted in a 46 ± 3% reduction in skin wheal size compared with untreated controls. The same intravenous dose of **10** in this test gave an 88 ± 12% decrease in skin wheal size. Thus, **25** is capable of blocking $LTE_4$-related symptomology in vivo, although it is less active than **10**.

In conclusion, we have defined the structural parameters among a series of basic ester and amide derivatives of 2-substituted pyrido[2,1-*b*]quinazoline derivatives necessary for the prevention of SRS-A-induced constrictions in vitro. In addition, we have demonstrated the intravenous activity of the phenylpiperazine **25** in two animal models developed for examining the ability of compounds to block SRS-A-related symptomatology in vivo. Although these compounds were all considerably less active than the standard reference antagonist, **10**, they represent a new structural class of compound that exhibits SRS-A antagonism. In future papers in this series, we will describe the synthesis and evaluation of more potent and orally active compounds in these test systems and other studies that have been conducted to further define the mechanism of action of these compounds.

## Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectral data (IR, MS, and NMR) were recorded for all new compounds and were in accord with the assigned structures. Microanalytical data were determined for C, H, N, and, where appropriate, Cl and S on all new compounds and agree to within ±0.4% of the calculated values, except as indicated.

**Method A. 2-(Diethylamino)ethyl 2-(1-Methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylate (2).** A suspension of 36.6 g (0.21 mol) of 2-(diethylamino)ethyl chloride hydrochloride in 200 mL of 2 M sodium hydroxide solution was extracted with 3 × 300 mL of ether. The combined organic layers were dried ($K_2CO_3$) and evaporated at room temperature. The residual oil was combined with 24.1 g (0.085 mol) of 2-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-b]-quinazoline-8-carboxylic acid[1] (**1**) in 240 mL of isopropyl alcohol, and the resulting suspension was heated to reflux for 3 h, cooled, and filtered to give 34.16 g (96%) of **2**, mp 220–221 °C. Recrystallization from ethanol and then from dichloromethane–ether gave 21.3 g (60%), mp 221–222 °C (Table I).

**Method B. 2-(Diethylamino)ethyl 2-Methyl-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylate (6).** A yellow suspension of 5.00 g (0.0197 mol) of 2-methyl-11-oxo-11*H*-pyrido-[2,1-*b*]quinazoline-8-carboxylic acid[1] in 100 mL of thionyl chloride was heated to reflux temperature for 3 h. The reaction mixture was evaporated, diluted with 50 mL of toluene, and evaporated to dryness. The resulting solid was suspended in 150 mL of toluene, and the mixture was treated with 4.0 mL (0.030 mol) of 2-(diethylamino)ethanol and heated to reflux overnight.

The mixture was diluted with 200 mL of dichloromethane, washed with saturated sodium bicarbonate solution, water, and brine, dried ($MgSO_4$), and evaporated. The resulting oil was acidified with 20 mL of 1.5 M methanolic hydrochloric acid, and the product was precipitated with 50 mL of ether. Recrystallization from ethanol–ether gave 5.62 g (73%) of **6**, mp 236–238 °C (Table I).

**Method C. Amyl 2-(1-Methylethyl)-11-oxo-11*H*-pyrido-[2,1-*b*]quinazoline-8-carboxylate (9).** A solution of 5.00 g (0.013 mol) of the free base of **2** in 20 mL of amyl alcohol was heated to reflux for 24 h. The cooled reaction mixture was diluted with ether, washed with water, and dried ($Na_2SO_4$). Evaporation gave a yellow solid, which was crystallized from hexane to give 3.18 g (69%) of **9**, mp 107–108 °C (Table I).

**Method D. *N*-[2-(Diethylamino)ethyl]-2-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxamide (11).** A suspension of 20.0 g (0.079 mol) of **1**[1] in 400 mL of thionyl chloride was heated to reflux for 3 h, and the excess reagent was removed in vacuo, followed by evaporation with three successive 100-mL portions of toluene. The resulting yellow solid was suspended in 400 mL of toluene and treated with 20 mL (0.142 mol) of *N,N*-diethylethylenediamine. The suspension was heated to reflux for 2.5 h and allowed to cool, and the precipitate was collected. This material was dissolved in methanol, acidified with methanolic hydrochloric acid, evaporated to dryness, and recrystallized twice from methanol–ether to give 14.55 g (45%) of **11**, mp 256–258 °C (Table II).

**Method E. *N*-[2-(4-Phenyl-1-piperazinyl)ethyl]-2-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxamide (25).** A solution of 5.00 g (0.0177 mol) of **1**,[1] 3.60 g (0.0177 mol) of 2-(4-phenyl-1-piperazinyl)ethylamine, and 4.87 g (0.0177 mol) of diphenylphosphoryl azide in 100 mL of dry dimethylformamide was cooled to −5 °C, and 2.50 mL (0.018 mol) of triethylamine was added. The reaction mixture was stirred at −5 °C for 3 h and allowed to warm to room temperature overnight. The resulting clear solution was diluted with 250 mL of water and extracted with 4 × 250 mL of dichloromethane. The combined organic layers were washed with 2 × 250 mL of water, dried ($K_2CO_3$), and evaporated to give 8.1 g of a yellow solid. Crystallization from dichloromethane–hexane gave 6.0 g (72%) of the free base of **25**, mp 173–175 °C. Anal. ($C_{28}H_{31}N_5O$) C, H, N. Conversion to the hydrochloride salt and recrystallization from ethanol gave 5.45 g (61%) of **25**, mp 246–247 °C (Table II).

***N,N*-Diphenylethylenediamine (29).** A solution of 17.0 g (0.073 mol) of 2-(diphenylamino)ethyl chloride[7] and 20.4 g (0.110 mol) of potassium phthalimide in 250 mL of dimethylformamide was heated to a bath temperature of 135 °C for 48 h. The reaction mixture was diluted with water and extracted with 4 × 150 mL of ether. The combined organic layers were washed with water, dried ($Na_2SO_4$), and evaporated to a yellow solid. Recrystallization from ether gave 14.7 g (58%) of 2-[2-(diphenylamino)ethyl]-1*H*-isoindole-1,3(2*H*)-dione (**28**), mp 106–107 °C. Anal. ($C_{22}H_{18}N_2O_2$) C, H, N.

A solution of 9.00 g (0.026 mol) of **28** and 5.1 mL (0.105 mol) of hydrazine hydrate in 200 mL of ethanol was heated to reflux for 3 h. After the solution was cooled, the precipitate was filtered off, and the residue obtained by evaporation of the filtrate was distilled. The fraction of bp 138–144 °C (0.15 mm) amounted to 4.4 g (76%) of **29**. Anal. ($C_{14}H_{16}N_2$) C, H, N.

**Method F. 2-(1-Methylethoxy)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acid (32).** A mixture of 5.00 g (0.0216 mol) of 2-amino-5-(1-methylethoxy)benzoic acid,[8] 3.6 g (0.023 mol) of 6-chloronicotinic acid, and 0.10 g of potassium iodide in 10 mL of triglyme was heated to a bath temperature of 150 °C for 21 h. The resulting solid was triturated with ethanol and dissolved in hot 2-propanol containing *N,N*-dimethylethanolamine (DMEA). The precipitate that formed after cooling was dissolved in 2-propanol–DMEA, and the product **32** was precipitated by the slow addition of dilute hydrochloric acid to give 2.03 g (32%), mp 278–279 °C (Table IV).

**Method G. 2-(2-Methylpropyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acid (34).** A solution of 4.9 g (0.025 mol) of 2-amino-5-(2-methylpropyl)benzoic acid[9] and 5.6 g (0.036 mol) of 6-chloronicotinic acid in 35 mL of ethylene glycol methyl ether containing 0.35 mL of formic acid was heated to reflux for 5 h as a precipitate formed. The precipitate, 3.4 g, mp 277–281 °C, was collected and dissolved in 70 mL of pyridine. After removal of 1.04 g of high-melting impurity, the filtrate was evaporated, and the residue was recrystallized from DMF–acetic acid to give 1.6 g (21%) of **34**, mp 297–299 °C (Table IV).

**Blockade of SRS-A-Related Effects.** The in vitro screening system employed was the guinea pig ileum bioassay method of Orange and Austen.[11] A 1.5-cm segment of ileum was removed from animals weighing 200–250 g and suspended in an organ bath containing 10 mL of Tyrodes solution with $10^{-6}$ M atropine sulfate and $10^{-6}$ M pyrilamine maleate. The bath was maintained at 37

°C and aerated with a mixture of 95% $O_2$ and 5% $CO_2$. Isotonic contractions of the ileum were elicited by using SRS-A, generated by challenging chopped lung fragments from actively sensitized guinea pigs with egg albumin, in vitro.[15] The dose of SRS-A that gave 50% of the maximal contraction was used for the assay. Test compounds were added to the organ bath 3 min prior to challenge with SRS-A. Three concentrations of the compound (giving inhibitory effects ranging between 10 and 90%) were tested in duplicate to generate a log dose–response graph from which an $IC_{50}$ was calculated. The reproducibility of this assay system is demonstrated by the fact that the average concentration to give 50% inhibition (with the standard error) for three separate determinations with **10**, a standard SRS-A antagonist, was $3.5 \pm 0.5 \times 10^{-8}$ M.

The ability of compounds to prevent SRS-A-related symptomatology in vivo was assessed in two model systems that employed chemically synthesized leukotriene $E_4$ ($LTE_4$).[13] In the first model, the inhibitory activity of the drug toward bronchoconstriction induced in guinea pigs by $LTE_4$ was studied. A maximally constrictory dose of $LTE_4$ was injected into animals pretreated for 5 min with propranolol (0.1 mg/kg, iv). The average bronchoconstriction (in centimeters) elicited in five animals pretreated intravenously for 30 s at 10 mg/kg prior to challenge with $LTE_4$ was compared to the average of that obtained in three control animals to determine the percent inhibition for the drug. In the second in vivo system, a drug was studied for its ability to inhibit $LTE_4$-induced skin wheal formation in rat. A dose of $LTE_4$ that gave a maximal wheal response was injected (in 0.05 mL of saline) intradermally into anesthetized rats pretreated for 30 min with 50 mg/kg of pyrilamine maleate and 4 mg/kg of methylsergide maleate (both administered intraperitoneally). The rats were then immediately treated with test drug (at 10 mg/kg, iv), followed by an intravenous injection of Evans blue (0.5%) into the tail vein of the animal. Thirty minutes later the animals were sacrificed, and the skin wheal size was measured. The average response in five animals (four intradermal injections per animal) treated with test compound was compared to that obtained in a similar group of control animals to determine the percent inhibition by the drug.

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**Registry No.** **1**, 68701-10-0; **1** acid chloride, 86921-96-2; **2**, 86921-97-3; **2**·HCl, 68701-48-4; **3**, 86921-98-4; **3**·HCl, 68701-41-7; **4**, 86921-99-5; **4**·HCl, 68701-26-8; **5**, 86922-00-1; **5**·HCl, 68892-69-3; **6**, 86922-01-2; **6**·HCl, 86922-02-3; **7**, 86922-03-4; **7**·2HCl, 86922-04-5; **8**, 86922-05-6; **8**·HCl, 86922-06-7; **9**, 86922-07-8; **11**, 86941-89-1; **11**·2HCl, 86922-08-9; **12**, 86922-09-0; **12**·2HCl, 86922-10-3; **13**, 86922-11-4; **13**·2HCl, 86922-12-5; **14**, 86922-13-6; **14**·2HCl, 86922-14-7; **15**, 86941-90-4; **15**·2HCl, 86941-91-5; **16**, 86922-15-8; **16**·2HCl, 86922-16-9; **17**, 86922-17-0; **17**·2HCl, 86922-18-1; **18**, 86922-19-2; **19**, 86922-20-5; **19**·2HCl, 86922-21-6; **20**, 86922-22-7; **20**·2HCl, 86922-23-8; **21**, 86922-24-9; **21**·2HCl, 86922-25-0; **22**, 86922-26-1; **22**·2HCl, 86922-27-2; **23**, 86922-28-3; **23**·2HCl, 86922-29-4; **24**, 86922-30-7; **24**·3HCl, 86922-31-8; **25**, 86922-32-9; **25**·HCl, 86922-33-0; **26**, 86922-34-1; **26**·3HCl, 86922-35-2; **27**, 86922-36-3; **27**·HCl, 86922-37-4; **28**, 86922-38-5; **29**, 1140-29-0; **30**, 86922-39-6; **30**·HCl, 68700-97-0; **31**, 86922-40-9; **31**·2HCl, 86922-41-0; **32**, 68701-04-2; **33**, 68701-07-5; **34**, 86922-42-1; **34** acid chloride, 86922-43-2; **35**, 86922-44-3; **35** acid chloride, 86922-45-4; **36**, 86922-46-5; **36** acid chloride, 86922-47-6; 2-methoxy-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acid, 63094-36-0; 2-methyl-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acid, 63094-33-7; 2-(diethylamino)ethyl chloride hydrochloride, 869-24-9; 2-(diethylamino)ethanol, 100-37-8; *N*-(2-hydroxyethyl)piperidine, 3040-44-6; *N*,*N*-diethyl-2-hydroxypropylamine, 4402-32-8; amyl alcohol, 71-41-0; *N*,*N*-diethylethylenediamine, 100-36-7; *N*,*N*-dimethylethylenediamine, 108-00-9; *N*,*N*-diisopropylethylenediamine, 121-05-1; *N*,*N*-dicyclohexylethylenediamine, 50331-65-2; *N*,*N*-diethylpropylenediamine, 104-78-9; 2-piperidinoethylamine, 27578-60-5; 2-(2,2,6,6-tetramethylpiperidino)ethylamine, 828-55-7; 2-(4-phenylpiperidino)ethylamine, 41914-43-6; 2-(4-benzylpiperidino)ethylamine, 25842-32-4; 2-(4-methylpiperazin-1-yl)-ethylamine, 934-98-5; 2-(4-phenylpiperazin-1-yl)ethylamine, 21091-61-2; 2-[(4-diphenylmethyl)piperazin-1-yl]ethylamine, 24252-67-3; *N*-phenylethylenediamine, 1664-40-0; 2-(diphenylamino)ethyl chloride, 42393-65-7; potassium phthalimide, 1074-82-4; 8-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-2-carboxylic acid, 68700-95-8; 8-(1-methylethyl)-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-2-carbonyl chloride, 86922-48-7; 2-amino-5-(1-methylethoxy)benzoic acid, 68701-42-8; 2-amino-5-(2-methylpropyl)benzoic acid, 79069-39-9; 2-amino-5-(methylthio)benzoic acid, 76745-74-9; 2-amino-5-(1-methylpropyl)benzoic acid, 18331-74-3; 2-amino-5-(1,1-dimethylethyl)benzoic acid, 2475-77-6; 6-chloronicotinic acid, 5326-23-8.