action of the nitro compounds is different from that of the other compounds. The present NQR studies do not yield information on which a unique explanation for the deviation can be based.

From Figures 1–3 it can be seen that there is a significant correlation between ν_d, which is a measure of the ($\sigma_{NH} - \sigma_{NS}$) electron density at the sulfamyl nitrogen (see eq 8), and the in vitro carbonic anhydrase inhibitory activity of the benzenesulfonamides, with the exception of the nitro compounds. It appears that an increase of σ_{NH} or a decrease of σ_{NS} (or both) results in increased activity.

It has been postulated[23] that the carbonic anhydrase inhibitors attach themselves to the active site of the enzyme through hydrogen bonds formed by the N–H bonds of the sulfamyl group. A hydrogen bond of the type N–H···X, where X is a proton acceptor, results in an increase in the value of σ_{NH}. Thus, σ_{NH} can be taken to be a measure of the strength of the hydrogen bond formed by the N–H bond. The correlation between ν_d, which is a measure of $\sigma_{NH} - \sigma_{NS}$ electron density, and the carbonic anhydrase inhibitory activities of the benzenesulfonamides suggests the possibility that the activities of the sulfonamides parallel the strength of the hydrogen bonds formed between the N–H bonds of the sulfamyl group and the active site of the enzyme.

Conclusion

Nitrogen-14 NQR studies of several benzenesulfonamides in their solid state reveal significant correlations between the $\sigma_{NH} - \sigma_{NS}$ electron density at the sulfamyl nitrogen and the in vitro carbonic anhydrase inhibitory activities of the sulfonamides. It appears that the activities of the sulfonamides depend largely upon the electronic property of the sulfamyl group. The nitro compounds show considerable deviation from the expected trend. This cannot be explained by invoking the presence of hydrogen bonds in these compounds. The deviations are probably due to increased resonance conjugation between the nitro group and the sulfamyl group or to a different mode of action.

Acknowledgment. This research was supported by the United States Public Health Service, Research Grant GM19018-12, from the National Institute of General Medical Sciences.

References and Notes

(1) K. H. Beyer and J. E. Baer, *Pharmacol. Rev.*, **13**, 517 (1961).
(2) G. DeStevens, "Diuretics", Academic Press, New York, N.Y., 1963.
(3) T. Mann and D. Keilin, *Nature (London)*, **146**, 164 (1940).
(4) H. A. Krebbs, *Biochem. J.*, **43**, 525 (1948).
(5) N. Kakeya, N. Yata, A. Kamada, and M. Aoki, *Chem. Pharm. Bull.*, **17**, 1010, 2558 (1969).
(6) E. A. C. Lucken, "Nuclear Quadrupole Coupling Constants", Academic Press, London, 1969.
(7) E. Schempp and P. J. Bray, *Phys. Chem.*, **4**, 522.
(8) M. Bloom, E. L. Hahn, and B. Herzog, *Phys. Rev.*, **97**, 1699 (1955).
(9) G. L. Petersen, Ph.D. Thesis, Brown University, 1975.
(10) Nicolet Instrument Corporation, Model 527.
(11) S. N. Subbarao and P. J. Bray, *J. Chem. Phys.*, **67**, 3947 (1977).
(12) H. A. Levy, S. W. Peterson, and J. E. Worshaw, Oak Ridge National Laboratory Report 1755, 1954.
(13) C. C. Costain and J. M. Dowling, *J. Chem. Phys.*, **32**, 158 (1960).
(14) D. G. Lister and J. K. Tyler, *Chem. Commun.*, **6**, 152 (1966).
(15) C. H. Townes and B. P. Dailey, *J. Chem. Phys.*, **17**, 782 (1949).
(16) E. Schempp and P. J. Bray, *J. Chem. Phys.*, **49**, 3450 (1968).
(17) W. H. Miller, A. M. Dessert, and R. O. Roblin, Jr., *J. Am. Chem. Soc.*, **72**, 4893 (1950).
(18) K. N. Trueblood, E. Goldish, and J. Donohue, *Acta Crystallogr.*, **14**, 1009 (1961).
(19) A. C. Skapski and J. L. Stevenson, *J. Chem. Soc., Perkin Trans. 2*, **8**, 1197 (1973).
(20) A. Pullman and H. Berthod, *Theor. Chim. Acta*, **10**, 461 (1968).
(21) F. A. Momany, R. F. McGuire, J. F. Yan, and H. A. Scheraga, *J. Phys. Chem.*, **74**, 2424 (1970).
(22) R. W. Taft, Jr., N. C. Deno, and P. S. Skell, *Annu. Rev. Phys. Chem.* **9**, 287 (1958).
(23) Y. Shinagawa and Y. Shinagawa, *Int. J. Quantum Chem.* **8**, 169 (1974).

11-Oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acid, an Orally Active Antiallergy Agent

Charles F. Schwender,* Brooks R. Sunday,

Department of Chemistry

and David J. Herzig

Department of Pharmacology, Warner-Lambert/Parke-Davis, Pharmaceutical Research Division, Ann Arbor, Michigan 48106.
Received August 3, 1978

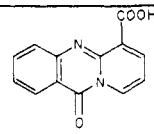
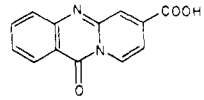
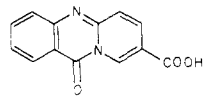
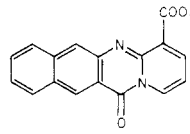
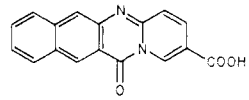
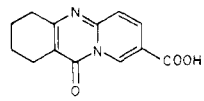
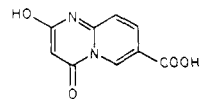
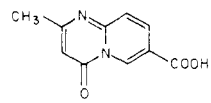
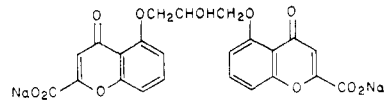
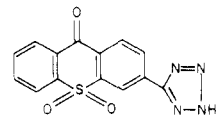
A new series of 11-oxo-11*H*-pyrido[2,1-*b*]quinazolinecarboxylic acids and related analogues has been synthesized and evaluated as potential antiallergy agents. In the rat PCA test, 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acid is orally active and more potent than cromolyn sodium or doxantrazole intravenously.

Some 11-oxo-11*H*-pyrido[2,1-*b*]quinazolinecarboxylic acids have been synthesized and evaluated as potential antiallergy agents. Their activities were compared with two clinically active agents, cromolyn sodium and doxantrazole. While cromolyn sodium is ineffective orally, it is useful when insufflated as a powder. Doxantrazole was reported to be orally active in early single-dose clinical trials.[1,2]

The reversible narrowing of bronchial airways and accompanying edema in bronchial mucosa observed in

0022-2623/79/1822-0114$01.00/0

Table I. Inhibition of Rat PCA by Pyrido[2,1-*b*]quinazoline Analogues

compd	structure	formula	rat PCA test: % inhib, 0.5 mg/kg, iv	rat PCA test: ID_{50}, mg/kg[a] iv	rat PCA test: ID_{50}, mg/kg[a] po
1		$C_{13}H_8N_2O_3$[b]	inactive		
2		$C_{13}H_8N_2O_3$	21%		
3		$C_{13}H_8N_2O_3 \cdot HCl$[c]	45	0.5	2.5
4		$C_{17}H_{10}N_2O_3$	inactive		
5		$C_{17}H_{10}N_2O_3$	100	0.1[d]	inactive[d]
6		$C_{13}H_{12}N_2O_3$	inactive		
7		$C_9H_6N_2O_4$	26% at 5 mg		
8		$C_{10}H_8N_2O_3$	inactive		
cromolyn sodium				1-2	inactive
doxantrazole				1.5	5

[a] Dose required to achieve 50% inhibition in PCA test. [b] Compound cited in ref 3. [c] Compound cited in ref 4 and 5. [d] The potency of analogue **5** was reported in ref 10 as ED_{50} = 0.015 mg/kg, iv, and <0.1 mg/kg, po. However, after further evaluation, this potency was not consistent for all animals tested. The activity reported here is a more conservative value obtained after additional biological evaluation.

asthma may be caused by a specific allergic response or by a nonspecific irritant. β-Adrenergic bronchodilators, anticholinergics, theophylline, or steroids are used for symptomatic relief. An alternate approach involves the use of an antiallergy agent, such as cromolyn sodium, which appears to act by preventing the release of histamine and other possible allergic mediators resulting from antibody–antigen interactions.[1]

We report here the synthesis and antiallergy activity of 11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic acid (**3**) and related analogues.

Chemistry. The synthesis of 11-oxo-11*H*-pyrido-[2,1-*b*]quinazoline-7-carboxylic acid (**2**) was accomplished through the fusion[3] of methyl anthranilate with 2-chloropyridine-4-carboxylic acid at 175–195 °C. The 8-carboxylic isomer[4,5] **3**, as well as 6-oxo-6*H*-benzo[*g*]-pyrido[2,1-*b*]quinazoline-1-carboxylic acid (**4**), was obtained by refluxing anthranilic or 3-amino-2-naphthoic acid with 2-chloronicotinic acid in ethanol containing hydrochloric acid. Heating 6-aminonicotinic acid in glacial acetic acid with ethyl 2-oxocyclohexanecarboxylate or ethyl acetoacetate gave **6** and **8**, respectively.[6] Analogue **7** was obtained by heating diethyl malonate and 6-aminonicotinic acid in diphenyl ether.

Discussion

Compounds **1**–**8** were evaluated for their antiallergy activity by their ability to inhibit passive cutaneous anaphylaxis (PCA) in rats (see Table I), as described in the Experimental Section.[7] Those agents which showed an inhibition greater than 50% at 0.5 mg/kg iv were studied further for their ID_{50} iv and oral efficacy compared with cromolyn sodium and doxantrazole.

The analogues possessing significant inhibitory activity in the PCA test were **3** and **5**, while those remaining had little activity. Histamine-induced contractions of the guinea pig ileum were not antagonized by **3** or **5** in concentrations up to 10^{-4} M,[8] indicating that neither com-

pound was acting as a histamine antagonist.

The presence of benzo or naphtho substitution in the 4,5 positions of the pyrimidine ring imparted significant antiallergy potency. The optimal position for the carboxylic acid was the 8 isomer in the pyrido[2,1-*b*]-quinazoline, compound **3**, and the corresponding 3 isomer for the benzo[*g*]pyrido[2,1-*b*]quinazoline ring system of **5**. Intravenously, **5** was 10–20 times more potent than cromolyn sodium or doxantrazole. Compound **3** was five to ten times more potent than cromolyn and doxantrazole intravenously and possessed oral activity as well. Because of its oral activity, the synthesis and biological evaluation of additional analogues of **3** are in progress.

Experimental Section

Rat Reaginic Passive Cutaneous Anaphylaxis (PCA). The PCA test[7] involved immunization of rats with 1 mg of ovalbumin intramuscularly and approximately 10^{10} *B. pertussis* organisms as pertussis vaccine, intraperitoneally. Fourteen days later, the rats were bled and the serum was prepared. Suitable dilutions of antiserum were injected intradermally at various sites on the back of rats 48 h before an intravenous injection of 1 mg of ovalbumin in 1 mL of physiological saline and 0.25% Evans Blue. Thirty minutes later the animals were killed in ether, the dorsal skin was reflected, and the mean orthogonal diameter was measured. For oral 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 each spot 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:

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

The statistical significance of the results was determined by Student's *t* test ($p \leq 0.05$). An inhibition of 15% was significant.

Melting points were taken in open capillary tubes on a Mel-Temp and are uncorrected. Each analytical sample was homogenous by TLC and had IR, UV, and NMR spectra compatible with its structure. Combustion analysis for C, H, N, and Cl gave results within 0.4% of theory.

11-Oxo-11*H*-pyrido[2,1-*b*]quinazoline-6-carboxylic Acid (1). A mixture of 9.00 g (57.0 mmol) of 2-chloronicotinic acid, 23.0 g (139 mmol) of ethyl anthranilate, and 0.1 g (0.6 mmol) of KI was heated at 160 °C for 1.5 h with loss of EtOH.[3] The resultant orange cake was heated in hot EtOH (600 mL) and filtered. The cooled filtrate yielded 3.10 g (22.3%) of the analytically pure product, mp 222–223 °C.[3] Anal. ($C_{13}H_8N_2O_3$) C, H, N.

11-Oxo-11*H*-pyrido[2,1-*b*]quinazoline-7-carboxylic Acid (2). A mixture of methyl anthranilate (12.9 g, 85.4 mmol) and 2-chloropyridine-4-carboxylic acid[8] (4.74 g, 30 mmol) was heated at 175–195 °C for 1.5 h. The melt was cooled and triturated with MeOH, giving a yellow insoluble powder, mp 265–275 °C dec, which was recrystallized from pyridine and gave 1.55 g (21.5%) of a yellow crystalline material, mp 316–320 °C dec. Further recrystallizations of this material from pyridine gave 0.73 g (10.1%) of the analytical sample, mp 346–349 °C dec. Anal. ($C_{13}H_8N_2O_3$) C, H, N.

11-Oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acid Hydrochloride (3). A reaction mixture of 4.35 g (31.8 mmol) of anthranilic acid, 4.96 g (31.8 mmol) of 6-chloronicotinic acid, 3 mL (26.3 mmol) of concentrated HCl and 80 mL of EtOH was heated at reflux for 21 h. The mixture was cooled and filtered to give 3.40 g (38.9%) of the expected product, mp 323–325 °C dec. The analytical sample was obtained by recrystallization from MeOH–Et_2O, mp 323–325 °C dec.[4,5] The mp 318–319 °C was reported for the free acid.[4,5] Anal. ($C_{13}H_8N_2O_3$·HCl) C, H, N, Cl.

6-Oxo-6*H*-Benzo[*g*]pyrido[2,1-*b*]quinazoline-1-carboxylic Acid (4). An ethanolic mixture (180 mL) containing 5.00 g (26.8 mmol) of 3-amino-2-naphthoic acid, 4.21 g (26.8 mmol) of 2-chloronicotinic acid, and 2.1 mL (18.4 mmol) of concentrated HCl was heated at reflux for 72 h. The resultant suspension was cooled and yielded an orange-red powder upon filtration: yield 3.1 g (40.0%); mp 285–288 °C dec. Recrystallization of the crude product from DMF gave 2.21 g of the analytical sample, mp 284–285 °C dec. Anal. ($C_{17}H_{10}N_2O_3$) C, H, N.

6-Oxo-6*H*-benzo[*g*]pyrido[2,1-*b*]quinazoline-3-carboxylic Acid (5). A reaction mixture of 68.0 g (364 mmol) of 3-amino-2-naphthoic acid, 57.4 g (364 mmol) of 6-chloronicotinic acid, and 900 mL of glacial acetic acid was heated at reflux for 16 h. The reaction mixture was cooled to 25 °C and the precipitate which formed was collected to give 70.0 g (66.2%) of a yellow powder, mp 270–282 °C dec. The crude product was recrystallized twice from pyridine to give 29.1 g (27.6%) of yellow crystalline product in analytical purity, mp 375–384 °C dec. Anal. ($C_{17}H_{10}N_2O_3$) C, H, N.

1,2,3,4-Tetrahydro-11-oxo-11*H*-pyrido[2,1-*b*]quinazoline-8-carboxylic Acid (6). Ethyl 2-oxocyclohexanecarboxylate (4.94 g, 29.0 mmol) and 6-aminonicotinic acid (4.00 g, 29.0 mmol) were heated in refluxing glacial acetic acid (25 mL) for 72 h. The mixture was allowed to cool to room temperature, and the resultant precipitate was collected, giving 3.20 g (45.3%) of crude product, mp 240–244 °C dec. The crude **6** was recrystallized twice from pyridine, and the analytical sample was obtained: yield 1.10 g (15.6%); mp 259–261 °C dec. Anal. ($C_{13}H_{12}N_2O_3$) C, H, N.

3,4-Dihydro-2,4-dioxo-2*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylic Acid (7). A mixture of 1.00 g (7.25 mmol) of 6-aminonicotinic acid and 1.16 g (7.25 mmol) of diethyl malonate dissolved in diphenyl ether (25 mL) was heated at reflux for 1.5 h. The mixture was cooled and diluted with 30 mL of heptane, yielding a tan precipitate, yield 1.35 g (90.6%); mp 295–302 °C dec. The crude **7** was recrystallized from pyridine, and 0.71 g (47.7%) of the analytically pure sample of **7** was obtained, mp 339–343 °C dec. Anal. ($C_9H_6N_2O_4$) C, H, N.

2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-7-carboxylic Acid (8). A mixture of 5.00 g (36.2 mmol) of 6-aminonicotinic acid and 9.36 g (72.0 mmol) of ethyl acetoacetate was heated in 100 mL of refluxing glacial acetic acid for 30 h. EtOH (200 mL) was added to the mixture and cooled. The resultant precipitate was collected by filtration to yield 2.80 g (37.8%) of crude **8**, mp 259–280 °C dec. Recrystallization of this material from pyridine gave 0.85 g (11.5%) of the analytical sample, mp 278–282 °C dec. Anal. ($C_{10}H_8N_2O_3$) C, H, N.

Acknowledgment. The authors thank U. Zeek for the microanalyses.

References and Notes

(1) J. F. Batchelor, L. G. Garland, A. F. Green, M. J. Fallenfant, J. H. Gorvin, H. F. Hodson, and J. E. Tateson, *Lancet*, 1169 (1975).
(2) S. R. Walker, M. E. Evans, A. J. Richards, and J. W. Patterson, *J. Pharm. Pharmacol.*, **24**, 525 (1972).
(3) Netherlands Patent 6 414 717, June 21, 1965.
(4) E. Späth and F. Kuffner, *Ber. Dtsch. Chem. Ges.*, **71B**, 1657 (1938).
(5) A. Reissert, *Ber. Dtsch. Chem. Ges.*, **28**, 123 (1895).
(6) K. Bowden and T. H. Brown, *J. Chem. Soc. C*, 2163 (1971).
(7) D. J. Herzig, P. R. Schumann, E. J. Kusner, L. Robichaud, R. E. Giles, B. Dubnick, M. von Strandtmann, S. Kluchko, M. Cohen, and J. Shavel, Jr., "Immunopharmacology", M. E. Rosenthale and H. C. Mansmann, Eds., Spectrum Publications, Inc., New York, N.Y., 1975, pp 103–124.
(8) J. R. Petrillo and S. R. Smith, *Int. Arch. Allergy Appl. Immunol.*, **44**, 309 (1973).
(9) Y. Suzuki, *Yakugaku Zasshi*, 81, 1204 (1961).
(10) C. F. Schwender and B. R. Sunday, U.S. Patent 4 012 387, March 15, 1977.