contents of the flask, which had been cooled and maintained during the course of the addition in an EtOH/H_2O solution held at -15 °C. After 30 min, the cooling bath was recovered, and the contents of the flask were poured into a separating funnel and extracted 3 times with ice-cold H_2O (3 × 40 mL) to remove the phosphine oxide formed during the reaction. The CH_2Cl_2 layer was retained, dried thoroughly over anhydrous $MgSO_4$, and rotary evaporated to leave a viscous brown oil. This oil was shaken vigorously with Et_2O in which it appeared insoluble, and the resulting suspension filtered rapidly under vacuum. The Et_2O filtrate was saved and stored overnight at -30 °C to yield as a precipitate 0.62 g of 4 (0.001 mol, 25%): fine, cream-white crystals; mp >300 °C (with decomposition); IR (Nujol) ν_{max} 1610 (biphenyl), intense bands 1310, 1250 (alkyl ether), 1080, 1060 (morpholinium ether), 830 (*p*-phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (s, 8 H, aromatic), 4.35–3.85 (m, 4 H, methylene adjacent to morpholine oxygen), 3.62–3.35 (m, 8 H, ethoxy methylene and methylenes adjacent to bromine), 3.31–2.15 (overlapping signals, 12 H, methylenes adjacent to nitrogen), 1.23 (t, 6 H, ethoxy methyl). Anal. ($C_{28}H_{38}Br_2N_2O_4$) C, H, N.

2,2-(4,4-Biphenylene)bis[2-hydroxy-4-(2-bromoethyl)morpholine] (HC3-BrM, 5). The hydrochloride salt of 4 (100 mg, 1.5 × 10^{-4} mol) was dissolved in 20 mL of H_2SO_4 (1 M), and the solution was stirred at room temperature for 4 h. The mixture was placed on ice, neutralized with NaOH (5 M), and rapidly extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried over anhydrous $MgSO_4$, rotary evaporated to a pale yellow oil, and dissolved in Na-dried benzene. The addition of dry HCl precipitated the hydrochloride salt of **5** (HC3-BrM·2HCl) (25 mg, 4.1 × 10^{-5} mol, 27%): IR (Nujol) ν_{max} 3500–3100 (associated hydroxy), 1670 (very weak, phenyl carbonyl), 1610 (biphenyl), 1070, 1060 (mopholinium ether), 815 (*p*-phenyl) cm^{-1}; ^1H NMR (Me_2CO-d_6) δ 7.9–7.78 (m, 8 H, aromatic), 4.36–3.8 (m, 4 H, methylene adjacent to morpholine oxygen), 3.76–3.5 (overlapping signals, 6 H, methylenes adjacent to bromine and including hydroxyprotons), 3.0–2.26 (overlapping signals, 12 H, methylenes adjacent to nitrogen). Anal. ($C_{24}H_{32}Br_2Cl_2N_2O_4$) C, H, N.[22]

2-Phenyl-2-ethoxy-4-(2-hydroxyethyl)morpholine (9). Phenacyl bromide (50 g, 0.185 mol) in 250 mL of EtOH was added with stirring to diethanolamine (31.5 g, 0.333 mol) dissolved in 50 mL of EtOH, and the resulting solution was refluxed for ~3 h. Following this, the acetal base **9** was obtained by a repeat of the extraction procedure for **2**. Solution of **9** in ethanolic HCl and addition of Et_2O resulted in precipitation of the hydrochloride salt: yield 24 g (0.083 mol, 33%); mp 124–126 °C. Anal. ($C_{14}H_{22}ClNO_3$) C, H, N.

2-Phenyl-2-ethoxy-4-(2-bromoethyl)morpholine (10). The procedure was similar to that outlined in the synthesis of **4**. Compound **9** (2.5 g, 0.01 mol) was dissolved with $CHBr_3$ (3.5 g, 0.014 mol) in CH_2Cl_2, and tris(dimethylamino)phosphine (1.95 g, 0.12 mol) was added. Treatment of the ethereal extract of the product with dry HCl resulted in a precipitate of **10**·HCl: yield 1.3 g (0.004 mol, 37%); mp 114–116 °C; IR of the HCl salt (Nujol) ν_{max} 2450 (tertiary amine HCl), 1250, 1165 (intense bands, alkyl ether), 1090, 1050 (morpholinium ether), 755, 700 (monosubstituted phenyl) cm^{-1}; ^1H NMR of free base ($CDCl_3$) δ 7.7–7.45 (m, 2 H, aromatic), 7.45–7.25 (m, 3 H, aromatic), 4.3–3.8 (m, 2 H, methylene adjacent to morpholine oxygen), 3.63 (t, 2 H, aminoethanol methylene adjacent to bromine), 3.6–2.08 (overlapping signals, 8 H, ethoxy methylene and methylenes adjacent to nitrogen), 1.20 (t, 3 H, ethoxy methyl). Anal. ($C_{14}H_{21}BrClNO_2$) C, H, N.

2-Phenyl-2-hydroxy-4-(2-bromoethyl)morpholine (HC15-BrM, 11). **10**·HCl (0.35 g, 0.001 mol) was treated with 20 mL of H_2SO_4 (1 M) in a procedure identical with that outlined for the preparation of HC3-BrM·2HCl. The yield of **11**·HCl was 0.16 g (5 × 10^{-4} mol, 50%): mp 127–128 °C; IR (Nujol) ν_{max} 3450 (associated hydroxy), 1680 (weak, phenyl carbonyl), 1070 (morpholinium ether), 760, 710 (monosubstituted phenyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.7–7.45 (m, 2 H, aromatic), 7.43–7.20 (m, 3 H, aromatic), 4.4–3.45 (overlapping signals, 5 H, hydroxy, methylene adjacent to morpholine oxygen, methylene adjacent to bromine), 2.9–2.1 (overlapping signals, 6 H, methylenes adjacent to nitrogen). Anal. ($C_{12}H_{17}BrClNO_2$) C, H, N.

Storage and Cyclization Titer Values of HC3-BrM (5) and HC15-BrM (11). Hemicholinium-3 bromo mustard (**5**) was made up as a 1 mM solution of the dihydrochloride salt in 0.1 M HCl and stored frozen in 1-mL aliquots at -20 °C. The rate and extent of ethylenimine ion formation by HC3-BrM was determined by the procedure of Gill and Rang.[23] Under these conditions, a 0.25 mM solution of HC3-BrM at pH 7.4 in 10 mM phosphate buffer yielded a maximal titration equivalent of 130% ethylenimine ion after 10 min at room temperature. For simplicity this can be interpreted as 65% of the molecules existing in the biethylenimine form (**6**), although in practice the true concentration of biethylenimine ion must lie between 30 and 65% of the initial mustard concentration. Under analagous circumstances, the monoethylenimine-forming HC15-BrM (**11**) exhibited a maximal ethylenimine ion (**12**) concentration of 75%.

Acknowledgment. The author thanks Drs. R. C. Hider and G. Arbuthnott for their help furing the course of this work. This work was financed by the Medical Research Council.

Registry No. 1, 312-45-8; **2**, 83291-87-6; **3**, 83291-89-8; **3**·HCl, 83291-88-7; **4**, 83291-90-1; **5**, 83291-91-2; **5**·2HCl, 79868-97-6; **6**, 79868-96-5; **7**, 4072-67-7; **8**, 4303-88-2; **9**·HCl, 83291-92-3; **10**·HCl, 83291-93-4; **11**, 83291-95-6; **11**·HCl, 83291-94-5; **12**, 83291-96-7; biphenyl, 92-52-4; bromoacetyl bromide, 598-21-0; diethanolamine, 111-42-2; phenacyl bromide, 70-11-1; choline, 62-49-7.

(22) N: calcd, 4.35 found, 3.86.

(23) E. W. Gill and H. P. Rang, *Mol. Pharmacol.*, **2**, 284 (1966).

Synthesis and Antiallergy Activity of 5-Oxo-5*H*-thiazolo[2,3-*b*]quinazolinecarboxylic Acids

Ronald A. LeMahieu,*[†] Mathew Carson,[†] Ann F. Welton,[‡] Herman W. Baruth,[‡] and Bohdan Yaremko[‡]

Chemical Research Department and Department of Pharmacology, Hoffmann-La Roche Inc., Nutley, New Jersey 07110.
Received May 24, 1982

A series of substituted 5-oxo-5*H*-thiazolo[2,3-*b*]quinazolinecarboxylic acids was prepared and evaluated in the rat PCA test for antiallergic activity. The analogues that exhibited the highest oral activity were the 7-methoxy, 7-methylthio, and 7-isopropyl in the 2-carboxylic acid series and the 2-isopropyl in the 7-carboxylic acid series.

Although numerous compounds that inhibit the release of mediators of anaphylaxis from sensitized mast cells have been described in the recent literature, disodium cromoglycate (DSCG) is the only drug of this type currently available for the prophylactic treatment of bronchial asthma. The major disadvantage of DSCG is that it is not active orally and must be taken by insufflation. Recently, DSCG has also become available in an aerosol formulation for inhalation.

[†] Chemical Research Department.
[‡] Department of Pharmacology.

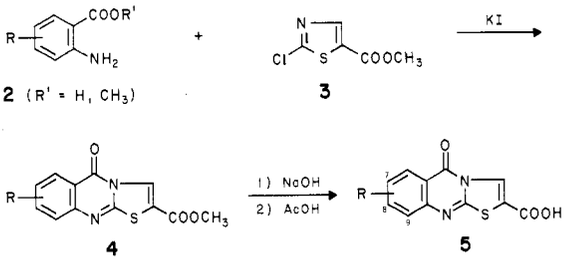
0022-2623/83/1826-0107$01.50/0

Table I. Methyl 5-Oxo-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxylates (4)

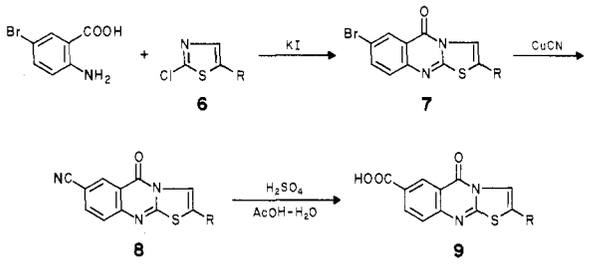
no.	R	formula	mp, °C	yield, %	method	recrystn solvent	anal.
4a	H	$C_{12}H_8N_2O_3S$	178-179	56	B	CH_2Cl_2-MeOH	C, H, N, S
4b	7-OCH_3	$C_{13}H_{10}N_2O_4S$	187-189	36	A	CH_2Cl_2-Et_2O	C, H, N, S
				65	B		
4c	7-SCH_3	$C_{13}H_{10}N_2O_3S_2$	195-198	74	A	CH_2Cl_2-Et_2O	C, H, N, S
				64	B		
4d	7-$CH(CH_3)_2$	$C_{15}H_{14}N_2O_3S$	114-118	45[a]	A		
4e	7-c-C_3H_5	$C_{15}H_{12}N_2O_3S$	*a*	12[a]	A		
4f	7-$CH_2CH(CH_3)_2$	$C_{16}H_{16}N_2O_3S$	132-134	59	B	MeOH	C, H, N, S
4g	7-$CH(CH_3)CH_2CH_3$	$C_{16}H_{16}N_2O_3S$	128-129	39	B	MeOH	C, H, N, S
4h	7,8-$(OCH_3)_2$	$C_{14}H_{12}N_2O_5S$	260-262	70	B	CH_2Cl_2-MeOH	C, H, N, S
4i	7,9-$[CH(CH_3)_2]_2$	$C_{18}H_{20}N_2O_3S$	148-153	31[a]	B		

[a] These compounds were not obtained completely pure.

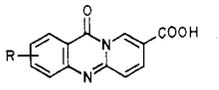
Scheme I



Scheme II



Several recent publications have appeared on the pyrido[2,1-*b*]quinazolinecarboxylic acids (**1**), which are orally

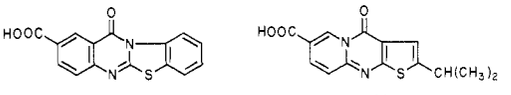


1, R = 2-OCH_3, 2-$CH(CH_3)_2$

active antiallergy agents in animal models.[1,2] In this paper we describe the synthesis of bioisosteres of **1**, the 5-oxo-5*H*-thiazolo[2,3-*b*]quinazolinecarboxylic acids,[3] which also exhibit oral antiallergy activity. Some 5-oxo-5*H*-thiazolo[2,3-*b*]quinazolines have been described in the literature,[4] and ethyl 5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-7-carboxylate is disclosed in a patent as an antiallergy agent.[5]

Chemistry. The 5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxyic acids (**5**, Scheme I, Table II) were prepared by condensation of substituted anthranilic acids or esters **2** with methyl 2-chlorothiazole-5-carboxylate (**3**),[6] either neat in the presence of potassium iodide at about 160 °C (method A) or in refluxing 2-methoxyethanol containing formic acid (method B). Basic hydrolysis of the resultant esters (**4**, Table I) with excess sodium hydroxide also opened the lactam ring, which was conveniently reclosed by crystallization from acetic acid to give the desired acids (**5**). Hydrolysis of the esters (**4**) with only a slight excess of sodium hydroxide proceeded more slowly but without opening of the lactam ring as described under Experimental Section for **5b**. Use of 2-chlorothiazole-5-carboxylic acid instead of the methyl ester gave the acids **5** directly, but, in the few cases tried, yields were lower than in the two-step procedure. The sulfoxide **5d** was prepared by oxidation of the corresponding methylthio compound with sodium periodate.

The 5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-7-carboxylic acid (**9**, Scheme II, Table III) were prepared by condensation of 5-bromoanthranilic acid with the 2-chlorothiazoles (**6**) to provide the bromo compounds (**7**), which gave the nitriles (**8**) on treatment with cuprous cyanide in refluxing DMF.[7] The intermediates **7** and **8** were not completely characterized. The nitriles were converted to the desired acids (**9**) by acid hydrolysis. Compound **10** was prepared from 2-chlorobenzothiazole in an analogous fashion. The antiallergy activity of a series of 4-oxo-4*H*-pyrido[1,2-*a*]-thieno[2,3-*d*]pyrimidines was reported recently,[8] and one of these compounds, **11**, was prepared to compare activities.



Biological Results and Discussion

The compounds described were evaluated for antiallergy activity in the rat passive cutaneous anaphylaxis (PCA) test,[2] and the results are reported in Tables II and III. High oral activity was found for derivatives substituted with methoxy, methylthio, and branched alkyl substituents. The most potent compounds were **5b**,**c**,**e** and **9c**. The methyl ester **4b** was substantially less active (39% inhibition at 16 mg/kg ip) than the corresponding acid. Oxidation of the methylthio substituent to methylsulfinyl caused a decrease in activity. Compounds **5e** and **9c** exhibited approximately the same activity, indicating that the nitrogen atom in the 4-position and the sulfur atom

(1) C. F. Schwender, B. R. Sunday, D. J. Herzig, E. K. Kusner, P. R. Schumann, and D. L. Gawlak, *J. Med. Chem.*, **22**, 748 (1979).
(2) J. W. Tilley, R. A. LeMahieu, M. Carson, R. W. Kierstead, H. W. Baruth, and B. Yaremko, *J. Med. Chem.*, **23**, 92 (1980).
(3) R. A. LeMahieu, U.S. Patents 4 168 380 and 4 282 360 (1979).
(4) G. Singh, H. S. Sachdev, and K. S. Narang, *J. Sci. Ind. Res.*, **16B**, 359 (1957).
(5) K. Schromm, A. Mentrup, E.-O. Renth, and A. Fügner, U.S. Patent 4 083 980 (1978).
(6) H. Erlenmeyer, P. Buchmann, and H. Schenkel, *Helv. Chim. Acta*, **27**, 1432 (1944).
(7) L. Friedman and H. Schechter, *J. Org. Chem.*, **26**, 2552 (1961).
(8) F. J. Tinney, W. A. Cetenko, J. J. Kerbleski, D. T. Connor, R. J. Sorenson, and D. J. Herzig, *J. Med. Chem.*, **24**, 878 (1981).

Table II. 5-Oxo-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxylic Acids (5)

no.	R	formula	mp, °C	recrystn solvent	yield, %	anal.	rat PCA test[a]		
							% inhibn,[b] 16 mg/kg ip	% inhibn,[b] 32 mg/kg po	ID_{50},[c] mg/kg po
5a	H	$C_{11}H_6N_2O_3S$	244–245	HOAc	59	C, H, N, S	80 ($p > 0.005$)		
5b	7-OCH_3	$C_{12}H_8N_2O_4S$	248–249	pyridine	81	C, H, N, S	100	78	0.07 (0.04–0.14)
5c	7-SCH_3	$C_{12}H_8N_2O_3S_2$	253–255	HOAc	77	C, H, N, S		87	0.12 (0.07–0.23)
5d	7-$SOCH_3$	$C_{12}H_8N_2O_4S_2$	245–246	HOAc	77	C, H, N, S	55	67[d]	1.82 (0.98–4.02)
5e	7-$CH(CH_3)_2$	$C_{14}H_{12}N_2O_3S$	235–237	MeOH–H_2O	50	C, H, N, S	89	86	0.33 (0.18–0.61)
5f	7-c-C_3H_5	$C_{14}H_{10}N_2O_3S$	257–259	HOAc	80	C, H, N, S		100[d]	6.02 (2.14–29.01)
5g	7-$CH_2CH(CH_3)_2$	$C_{15}H_{14}N_2O_3S$	233–235	HOAc	80	C, H, N, S	62	78[d]	2.12 (0.89–6.85)
5h	7-$CH(CH_3)CH_2CH_3$	$C_{15}H_{14}N_2O_3S$	215–217	HOAc	89	C, H, N, S	59	64[d]	1.01 (0.58–1.91)
5i	7,8-$(OCH_3)_2$	$C_{13}H_{10}N_2O_5S$	276–277	HOAc	86	C, H, N, S	89		
5j	7,9-$[CH(CH_3)_2]_2$	$C_{17}H_{18}N_2O_3S$	221–223	MeOH–H_2O	87	C, H, N, S	100	79	>10
disodium cromoglycate							46 (8 mg/kg)	18[d]	

[a] As described in ref 2 with a 5-min pretreatment time. [b] $p < 0.001$ using Student's t test except as noted. [c] Numbers in parentheses represent Fieller's 95% confidence limits. [d] Ten-minute pretreatment time.

are not important receptor binding sites. The benzothiazolo analogue **10** was inactive at 16 mg/kg ip, and the known[8] pyrido[1,2-*a*]thieno[2,3-*d*]pyrimidine **11** was substantially less active orally than **9c**.

Compounds **5b** and **5c** were orally active (ID_{50} values of 1.20 and 0.03 mg/kg, respectively) in a model in which anaphylactic bronchospasm was studied in passively sensitized rats[9] and were potent inhibitors (IC_{50} values of 0.06 and 0.01 μM, respectively) of antigen-induced histamine release from passively sensitized rat peritoneal cells[10] in vitro.

In summary, the substituted 5-oxo-5*H*-thiazolo[2,3-*b*]-quinazolinecarboxylic acids represent a novel series of potent, orally active antiallergy agents.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Spectra data (IR, NMR, UV, and MS) were obtained for the new compounds and were in agreement with the assigned structures. Microanalytical data were obtained on all completely characterized new compounds and agree to within ±0.4% of the calculated values.

Methyl 7-Methoxy-5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxylate (4b). Method A. An intimate mixture of 9.00 g (0.054 mol) of 2-amino-5-methoxybenzoic acid, 9.56 g (0.054 mol) of methyl 2-chlorothiazole-5-carboxylate (ref 2 describes the corresponding ethyl ester), and 0.45 g (0.003 mol) of powdered potassium iodide was stirred and heated in an oil bath at 160–165 °C for 80 min. The resultant dark solid was treated with 200 mL of a saturated solution of $NaHCO_3$ and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated in vacuo to a brown solid (9.60 g). Recrystallization from CH_2Cl_2–Et_2O gave 5.65 g (36%), mp 187–189 °C, of **4b**. Anal. ($C_{13}H_{10}N_2O_4S$) C, H, N, S.

Method B. A solution of 13.6 g (0.075 mol) of 2-amino-5-methoxybenzoic acid, 13.3 g (0.075 mol) of methyl 2-chlorothiazole-5-carboxylate, and 1.5 mL of formic acid in 110 mL of 2-methoxyethanol was stirred at reflux for 2.5 h. While the solution was cooling to 25 °C, a yellow solid precipitated. Ether (100 mL) was added, and the solid was filtered and washed with ether to give 15.8 g of crude product. Recrystallization from CH_2Cl_2–Et_2O gave 12.2 g, mp 186–188 °C, of **4b** in the first crop. A second crop of 2.0 g, mp 185–187 °C, was obtained from the filtrate after two recrystallizations, making the total yield 65%.

7-Methoxy-5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxylic Acid (5b). A suspension of 13.77 g (0.048 mol) of **4b** and 52 mL (0.052 mol) of 1 N NaOH in 500 mL was stirred at room temperature for 2 h. The resultant suspension was concentrated in vacuo to remove the MeOH. Water (750 mL) was added, and the solution was extracted with CH_2Cl_2. the aqueous layer was acidified to pH 2.0, and the yellow solid was filtered and recrystallized from pyridine to give 10.80 g, mp 244–245 °C, after drying at 120 °C (0.1 mm) for 32 h. This solid was stirred for 15 min with 300 mL of water adjusted to pH 3.5. Filtration gave 10.55 g (81%), mp 248–249 °C, of **5b**. Anal. ($C_{12}H_8N_2O_4S$) C, H, N, S.

7-(Methylsulfinyl)-5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-2-carboxylic Acid (5d). To 1.02 g (0.0035 mol) of **5c** suspended in 25 mL of water was added 3.5 mL (0.0035 mol) of 1.0 N NaOH. The resultant solution was cooled in an ice bath and stirred while 0.82 g (0.00385 mol) of sodium periodate was added. The solution was stirred in the ice bath for 2 h and then at room temperature for 4 h. The mixture was cooled in an ice bath, and 3.8 mL of 1 N HCl was added with stirring. The solid was filtered and recrystallized from HOAc to yield 0.83 g (77%), mp 245–246 °C, of **5d**. Anal. ($C_{12}H_8N_2O_4S_2$) C, H, N, S.

2-(1-Methylethyl)-5-oxo-5*H*-thiazolo[2,3-*b*]quinazoline-7-carboxylic Acid (9c). An intimate mixture of 31.0 g (0.14 mol)

(9) R. A. Salvador, L. B. Czyzewski, H. Baruth, A. Hooper, A. Medford, D. Miller, T. VanTrabert, B. Yaremko, and A. F. Welton, *Agents Actions*, 11, 339 (1981).

(10) A. F. Welton, W. C. Hope, H. J. Crowley, and R. A. Salvador, *Agents Actions*, 11, 345 (1981).

Table III. 5-Oxo-5*H*-thiazolo[2,3-*b*]quinazoline-7-carboxylic Acids (9)

no.	R	formula	mp, °C	recrystn solvent	overall yield, %	anal.	rat PCA test: % inhibn 16 mg/kg ip	rat PCA test: % inhibn 32 mg/kg po	rat PCA test: ID_{50}, mg/kg po
9a	H	$C_{11}H_6N_2O_3S$	316–318	HOAc	16	C, H, N, S	62	66	>10
9b	CH_3	$C_{12}H_8N_2O_3S$	310–315	HOAc	8	C, H, N, S		79	>10
9c	$CH(CH_3)_2$	$C_{14}H_{12}N_2O_3S$	298–302	HOAc	36	C, H, N, S	100	100	0.11 (0.08–0.18)
11							89	54	

of 2-amino-5-bromobenzoic acid, 19.4 g (0.12 mol) of 2-chloro-5-(1-methylethyl)thiazole,[11] and 0.78 g (0.005 mol) of potassium iodide was stirred and heated at 160–170 °C (bath temperature) for 2 h. The mixture was cooled, and the dark residue was pulverized and stirred with 50 mL of cold $CHCl_3$. Filtration gave a brown hydrochloride, which was treated with 200 mL of saturated $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and concentrated in vacuo to a solid (14.5 g), which was recrystallized twice from CH_2Cl_2–Et_2O to give 9.7 g, mp 154–158 °C, of **7** [R = $CH(CH_3)_2$]. The initial $CHCl_3$ filtrate was washed with saturated $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated in vacuo to 18.0 g of red solid. This was combined with the mother liquors from the above $CHCl_3$ recrystallizations and chromatographed on 500 g of silica gel. Elution with 10% EtOAc–toluene gave 8.4 g, mp 154–158 °C, of **7** [R = $CH(CH_3)_2$], making the total yield 17.5 g (45%). Anal. ($C_{13}H_{11}BrN_2OS$) C, H, Br, N, S.

A solution of 16.5 g (0.05 mol) of **7** [R = $CH(CH_3)_2$] and 9.2 g (0.10 mol) of cuprous cyanide in 170 mL of anhydrous DMF was stirred at reflux for 16 h. Water (1.3 L) and 17 mL of ethylenediamine[7] were added, and the mixture was stirred and heated on a steam bath for 30 min. The mixture was cooled in an ice bath, and the solid was collected by filtration and washed successively with 25% aqueous ethylenediamine, water, warm 10% aqueous NaCN solution, and water to yield 9.9 g of crude nitrile **8** [R = $CH(CH_3)_2$]. The low-resolution mass spectrum showed the molecular ion at *m/e* 269.

A solution of 9.9 g (0.037 mol) of **8** [R = $CH(CH_3)_2$] in 100 mL of HOAc, 100 mL of concentrated H_2SO_4, and 100 mL of H_2O was stirred at reflux for 2 h. While the solution was cooled, 9.7 g, mp 297–301 °C, of **9c** crystallized. Recrystallization from HOAc gave 8.8 g (83%), mp 297–302 °C, of pure **9c**. Anal. ($C_{14}H_{12}N_2O_3S$) C, H, N, S.

12-Oxo-12*H*-benzothiazolo[2,3-*b*]quinazoline-2-carboxylic Acid (10). A mixture of 10.0 g (0.046 mol) of 2-amino-5-bromobenzoic acid, 12.0 g (0.069 mol) of 2-chlorobenzothiazole, 0.5 g of potassium iodide, and 8 mL of triglyme was stirred and heated at 150 °C for 4.5 h. The mixture was cooled, Et_2O was added, and the insoluble solid was filtered and recrystallized from DMF–H_2O to yield 12.6 g (83%), mp 229–231 °C, of 2-bromo-12-oxo-12*H*-benzothiazolo[2,3-*b*]quinazoline. Anal. ($C_{14}H_7BrN_2OS$) C, H, Br, N, S.

A solution of the above bromo compound (3.3 g, 0.01 mol) and 1.8 g (0.02 mol) of cuprous cyanide in 30 mL of anhydrous DMF was stirred at reflux for 20 h. Water (200 mL) and 5 mL of ethylenediamine were added, and the mixture was stirred and heated on a steam bath for 15 min. The mixture was cooled in an ice bath, and the solid was filtered and washed successively with 25% aqueous ethylenediamine, water, 10% NaCN, and water to give 2.4 g of crude nitrile.

A solution of the above nitrile (2.4 g) in 25 mL of HOAc and 50 mL of 50% H_2SO_4 was stirred at reflux for 90 min. The mixture was cooled, and the solid was filtered and recrystallized from DMF–H_2O to yield 1.8 g (70%), mp >300 °C, of **10**. Anal. ($C_{15}H_8N_2O_3S$) C, H, N, S.

Acknowledgment. We thank the staff of the Physical Chemistry Department of Hoffmann-La Roche Inc. for the determination of spectral and analytical data. We appreciate the guidance and encouragement of Dr. R. W. Kierstead during the course of this work.

Registry No. **2** (R = 5-OMe; R′ = H), 6705-03-9; **2** (R = 5-Br; R′ = H), 5794-88-7; **3**, 724605-86-8; **4a**, 83350-73-6; **4b**, 72605-87-9; **4c**, 78583-40-1; **4d**, 83350-74-7; **4e**, 83350-75-8; **4f**, 83350-76-9; **4g**, 83350-77-0; **4h**, 83350-78-1; **4i**, 83350-79-2; **5a**, 83350-80-5; **5b**, 72605-88-0; **5c**, 78583-41-2; **5d**, 78583-42-3; **5e**, 83350-81-6; **5f**, 83350-82-7; **5g**, 83350-83-8; **5h**, 83350-84-9; **5i**, 83350-85-0; **5j**, 83350-86-1; **6** [R = $CH(CH_3)_2$], 83350-90-7; **7** [R = $CH(CH_3)_2$], 83350-91-8; **8** [R = $CH(CH_3)_2$], 83350-92-9; **9a**, 83350-87-2; **9b**, 83350-88-3; **9c**, 83350-89-4; **10**, 83350-94-1; 2-chlorobenzothiazole, 615-20-3; 2-bromo-12-oxo-12*H*-benzothiazolo[2,3-*b*]quinazoline, 37752-72-0; 2-cyano-12-oxo-12*H*-benzothiazolo[2,3-*b*]quinazoline, 83350-93-0.

(11) G. Sunagawa, S. Okada, and H. Hamatsu, *J. Pharm. Soc. Jpn.*, **73**, 879 (1953).