In the case of the unsubstituted analogue diacetimide (1) possessed less hypocholesterolemic activity, i.e., 18%, than its cyclic congener, succinimide (6), i.e., 27%; however, dibenzimide (11) possessed greater hypocholesterolemic activity, i.e., 35% than its cyclic congener, diphenimide (14), i.e., 18%.

The ethyl-substituted propionic acids **5** and **10** possessed approximately the same magnitude of hypocholesterolemic activity (25–23%) after 16 days of dosing. It should be noted that the N-substitutions of butyl, butanone, and propionic acid did not dramatically increase the hypocholesterolemic activity of any of the four unsubstituted derivatives. *N*-(3-Oxobutyl)diacetimide (**3**), *N*-(2-carboxyethyl)succinimide (**9**), dibenzimide (**11**), and the butyl (**15**) and butanone (**10**) derivatives of diphenimide afforded the best hypocholesterolemic activity of each of the four series.

The opening of the cyclic imido ring system had a more consistent effect on hypotriglyceridemic activity. In most cases, the acyclic compound possessed reduced hypotriglyceridemic activity as compared to the respective cyclic compound.

Unsubstituted succinimide (**6**) resulted in 32% reduction of triglyceride levels whereas diacetimides only resulted in 2% reduction. The N-substitution of a propionic acid afforded the best hypotriglyceridemic activity of each of the series with **9** affording 44% and **4**, 21%. The *N*-(2-carboxyethyl) analogue (**9**) of succinimide was more effective than unsubstituted succinimide (**6**) by 12%. The same analogy also holds for the diacetimide series with the propionic acid demonstrating 19% improved activity over diacetimide itself. *N*-(3-Oxobutyl)dibenzimide (**13**) was the exception to the previous observation in that it demonstrated improved hypotriglyceridemic activity over N-(3-oxobutyl)diphenimide (**16**) by 29%. Nevertheless, diphenimide (**14**) and *N*-butyldiphenimide (**15**) were more active than their respective acyclic derivatives. Compound **15** was the most active in the triglyceride screen of the diphenimide series, affording 48% reduction. The intact imido ring does not appear to be necessary for hypocholesterolemic activity, whereas for hypotriglyceridemic activity, the closed rigid cyclic ring appears to be necessary.

Registry No. 1, 625-77-4; **2**, 1563-86-6; **3**, 92901-14-9; 4, 92901-15-0; **5**, 90609-20-4; **6**, 123-56-8; **7**, 3470-96-0; **8**, 77356-07-1; **9**, 5724-76-5; **10**, 81416-13-9; 11, 614-28-8; **12**, 73491-45-9; **13**, 92901-16-1; **14**, 3864-08-2; **15**, 92901-17-2; **16**, 92901-18-3; **17**, 92901-19-4; **18**, 85-41-6; *n*-butylamine, 109-73-9; acetic anhydride, 108-24-7; *N*-(3-oxobutyl)phthalimide, 3783-77-5; 1-aminobutan-3-one, 23645-04-7; β-alanine, 107-95-9; *N*-acetyl-β-alanine, 3025-95-4; β-alanine ethyl ester hydrochloride, 4244-84-2; succinic anhydride, 108-30-5; methyl vinyl ketone, 78-94-4; benzoyl chloride, 98-88-4; benzamide, 55-21-0; 1-aminobutan-3-one hydrochloride, 92901-20-7; *N*-benzoyl-1-aminobutan-3-one, 71666-56-3; diphenamic acid, 6747-35-9; diphenic anhydride, 6050-13-1.

2-(β-Arylethylamino)- and 4-(β-Arylethylamino)quinazolines as Phosphodiesterase Inhibitors

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The existence of several forms of cAMP phosphodiesterase having differing kinetic characteristics suggests the feasibility of developing tissue-selective inhibitors of this enzyme. This observation is of particular importance in the development of therapeutic agents for the management of reversible obstructive airways disorders. The present report describes the design, synthesis and pharmacological characterization of a series of 6,7-dimethoxyquinazoline derivatives having β-arylethylamine substituents at the 2- or 4-positions. The quinazoline nucleus is intended to confer a high degree of inhibitory activity for phosphodiesterase while the β-aryethylamine moieties are designed to provide selectivity for adrenergically innervated tissue. The target compounds of this study, **6** and **7**, were prepared via β-arylethylamine displacement of chloride from an appropriate chloroquinazoline intermediate. The resulting products were evaluated for their ability to relax guinea pig tracheal smooth muscle and as inhibitors of phosphodiesterase.

A major approach to the management of reversible obstructive airway diseases involves the use of agents capable of increasing the intracellular concentration of cyclic adenosine 3′,5′-monophosphate (cyclic AMP). Elevated cyclic AMP levels have been associated with both relaxation of airway smooth muscle[1,2] and inhibition of the release of histamine, leukotrienes, and other mediators of the anaphylactic response.[3,4] A significant research effort has been directed toward the development of β-sympathomimetic agents that stimulate the adenylate cyclase catalyzed synthesis of cyclic AMP.[5,6] Relatively less emphasis, however, has been placed on the development of agents that interfere with the catabolism of cyclic AMP via inhibition of phosphodiesterase. The observation that the enzyme exists in several forms having kinetic characteristics that vary from tissue to tissue[7] supports the feasibility of achieving tissue-selective inhibition of phosphodiesterase. The importance of cyclic nucleotides in modulating cellular function in virtually all mammalian tissues suggests that such selectivity of action is essential in order to obtain therapeutic agents with relatively few side effects.

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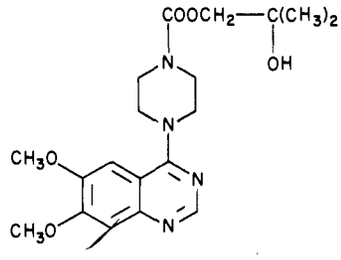
A variety of nitrogen- and oxygen-containing heterocycles are reported to inhibit phosphodiesterase.[1,2,8-11] The most common of these are the xanthine derivatives such as theophylline. Of interest to this research are those inhibitors characterized by a quinazoline ring. Phosphodiesterase inhibition has been suggested to be associated with numerous aminoquinazoline derivatives, including the bronchodilator hoquizil (**1**)[12] and the cardiac stimulant buquineran (**2**).[13] The antihypertensive agent prazosin (**3**), in addition to its action as an α_1-adrenolytic, is also



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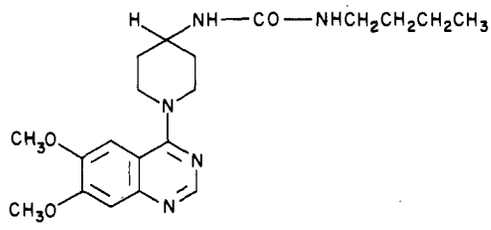

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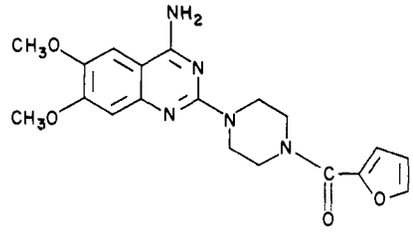

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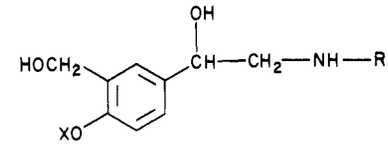
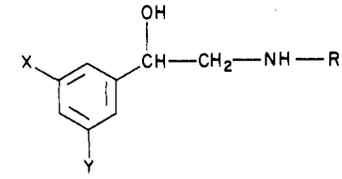
approximately equipotent with theophylline as an inhibitor of phosphodiesterase obtained from rat aorta.[14] The objective of the research described in this report is to investigate the effect of incorporating the aminoquinazoline heterocycle and various β-arylethanolamine moieties into a single molecule. A number of β-arylethanolamine derivatives, including the saligenin derivative albuterol (**4**) and the resorcinol derivative terbutaline (**5**), are associated with a selectivity for β_2-adrenoceptor agonism, the predominant β-receptor subtype found in bronchial tissue.[6] Thus, two series of aminoquinazolines, **6** and **7**, have been designed for this study involving progressive elaboration of the β-arylethylamine moiety. In addition, a diethylamino substituent was incorporated into the structures of **6** and **7**, in the 4- and 2-positions respectively, in an attempt to enhance the hydrophobicity of the target compounds in view of their intended intracellular site of action.



4, X = H; R = $C(CH_3)_3$
10, X = $CH_2C_6H_5$; R = H



5, X = Y = OH; R = $C(CH_3)_3$
12, X = Y = $OCH_2C_6H_5$; R = H
13, X = H; Y = $OCH_2C_6H_5$; R = H

Synthetic Procedures

The synthetic approach to **6** and **7** involved the treatment of an appropriate halogenated quinazoline derivative with a primary amine corresponding to the β-arylethylamine side chain. Consequently, the preparation of **6** and **7** consisted of three general steps: (1) preparation of the appropriate β-arylethanolamine with phenolic groups protected as benzyl ethers, (2) synthesis of the halogenated quinazoline precursors, and (3) nucleophilic displacement followed by, where applicable, removal of the benzyl protecting groups via catalytic hydrogenolysis.

Two general methods were employed in the preparation of the required β-arylethanolamines. The saligenin intermediate (**10**) was obtained from ethyl 5-acetyl-2-(benzyloxy)benzoate (**8**). Bromination of **8** provided the α-bromo ketone **9** along with the α,α-dibromo ketone as a minor impurity. The α-azido ketone, formed on treatment of **9** with NaN_3, was subsequently reduced to amino alcohol **10** with $LiAlH_4$. Amino alcohols **12** and **13** were obtained from the corresponding aldehydes by the method of Evans et al.[15] Thus, 3,5-bis(benzyloxy)benzaldehyde (**11**), prepared by pyridinium chlorochromate oxidation of the benzyl alcohol, was converted to the cyanohydrin ether by treatment with trimethylsilyl cyanide (Me_3SiCN) in the presence of a catalytic amount of ZnI_2. The cyanohydrin ether, without further purification, was reduced with $LiAlH_4$.

The dichloroquinazoline **14** proved to be a key intermediate in the preparation of **6** and **7** in view of the more facile nucleophilic displacement of chloride from the 4-position compared with the 2-position.[16] The intermediate **14** was prepared by a slight modification of the procedure of Hess et al.[17] In this method the immediate precursor to **14**, 6,7-dimethoxy-2,4-quinazolinedione, was obtained from 6,7-dimethoxyanthranilic acid in a manner that had previously been described by Curd et al.[18] The utility of **14** in the synthesis of the target compounds is illustrated in Scheme I. Treatment of **14** with diethylamine at room temperature afforded **15** exclusively. The isomeric derivative **17** was prepared by chlorination of quinazolinone **16**, which was obtained by base-catalyzed hydrolysis of **14**

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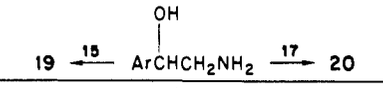
Table I. Properties of 19 and 20[a]



product	rctn condit	% yield	recrystn solvent	mp, °C	mol formula	anal.
19a	130 °C, 72 h	81	EtOH	202–203	$C_{29}H_{34}N_4O_4$·HCl	C, H, N
19b	130 °C, 57 h	78	EtOAc/Et_2O	159–160	$C_{36}H_{40}N_4O_5$·HCl	C, H, N
19c	115 °C, 60 h	83	EtOH	187–188	$C_{30}H_{36}N_4O_5$·HCl·H_2O	C, H, N
20a	110 °C, 36 h	61	EtOH/*i*-Pr_2O	221–222	$C_{29}H_{34}N_4O_4$·HCl	C, H, N
20b	110 °C, 60 h	85	EtOH/*i*-Pr_2O	141–143	$C_{36}H_{40}N_4O_5$·HCl·H_2O	C, H, N
20c	100 °C, 60 h	81	MeOH/Me_2CO	205–207	$C_{30}H_{36}N_4O_5$·HCl	C, H, N

[a] Ar = (a) 3-$C_6H_5CH_2OC_6H_4$, (b) 3,5-$(C_6H_5CH_2O)_2C_6H_3$, (c) 3-$HOCH_2$-4-$C_6H_5CH_2OC_6H_3$.

Table II. Properties of Phenolic Derivatives 6 and 7

compd	% yield	mp, °C	recryst solvent	formula	anal.
6c	77	230–231 dec	CH_3CN/H_2O	$C_{22}H_{28}N_4O_4$·HCl	C, H, N
6d	88	254–255	EtOH/10% HCl	$C_{22}H_{28}N_4O_5$·HCl·H_2O	C, H, N
6e	74	213–214	EtOH/Et_2O	$C_{23}H_{30}N_4O_5$·HCl	C, H, N
7c	85	156–158	MeOH/Et_2O	$C_{22}H_{28}N_4O_4$·HCl·H_2O	C, H, N
7e	59	265 dec	EtOH/Et_2O	$C_{23}H_{30}N_4O_5$·HCl·0.5H_2O	C, H, N

Table III. Pharmacological Properties of 6 and 7

	tracheal relaxation		phosphodiesterase inhibition		
compd	ED_{50} (95% CL), μM[a]	max relaxation obsd,[b] % (drug concn, μM)	IC_{50} (± 95% CL),[c] μM	K_i/K_m	type of inhib[d]
6a	234 (162–589)[e]		87 ± 14	0.054	competitive
6b	49.0 (33.1–91.2)[e,f]		328 ± 14	1.88	noncompetitive
6c		11.5 (84)[g]	295 ± 46	1.15	noncompetitive
6d	26.9 (23.4–30.9)		432 ± 36	0.43	noncompetitive
6e		36 (42)	339 ± 22	0.69	noncompetitive
7a		29 (70)[e,h]	16 ± 4	0.107	noncompetitive
7b		46 (98)[g]	350 ± 3	0.64	competitive
7c		28 (20)[g]	610 ± 105	0.73	competitive
7e	63.1 (52.5–75.9)[f]		428 ± 38	0.81	competitive
theophylline	70.8 (63.1–79.4)		1780 ± 90		competitive

[a] Concentration required to produce 50% of the maximal papaverine-induced relaxation. [b] Activity of compounds not attaining 50% of the maximal papaverine-induced relaxation is expressed as the maximum relaxation observed with the test compound (concentration of the test compound at which this relaxation occurred). [c] Concentration required to inhibit enzyme activity by 50%. [d] Range of cAMP concentrations was 0.075–0.60 mM. Double-reciprocal plots obtained with inhibitor were linear. [e] EtOH used to solubilize test compound. [f] Slope of log dose–response curve significantly different from that of theophylline ($P < 0.05$). [g] Me_2SO used to solubilize test compoun d. [h] Solubility limitation prevented testing at a higher concentration.

at room temperature followed by treatment with diethylamine at 130 °C. Evidence to support the structural assignments of **15** and **17** was obtained by examination of the proton-coupled ^{13}C NMR spectra as well as through the use of selective irradiation experiments.

Target compounds **6a** and **6b** were obtained directly from **15** by heating an ethanolic solution of **15** and phenethylamine or 2-amino-1-phenylethanol, respectively, in a sealed glass-lined metal reaction vessel. The preparation of **7a** involved a two-step procedure consisting of treatment of **14** with phenethylamine at room temperature to give **18**, followed by heating a mixture of **18** and diethylamine in a sealed reaction vessel. Although this approach proved useful for the synthesis of **7a**, it was less satisfactory for the preparation of the other members of this series. This prompted the use of **17** in the synthesis of target compounds in the 4-substituted series. Treatment of **17** with 2-amino-1-phenylethanol in refluxing THF provided **7b** in good yield.

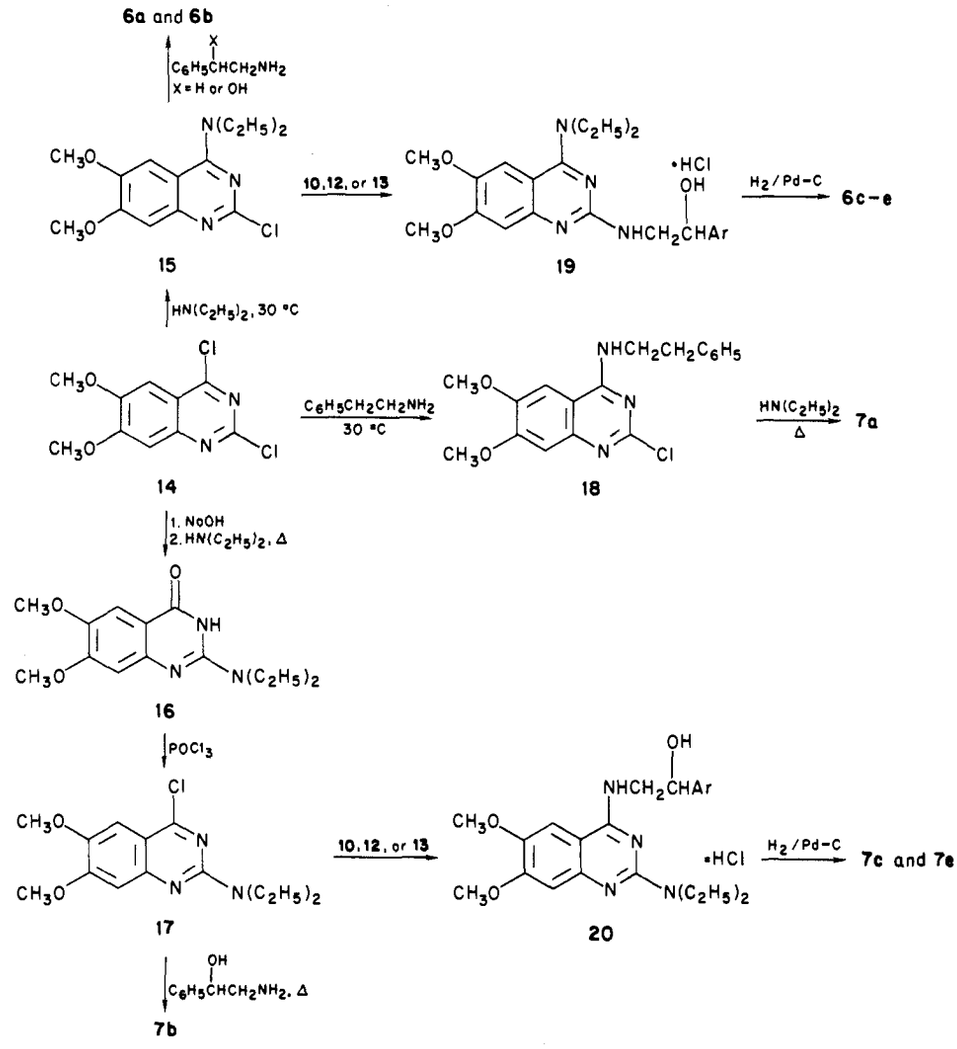
The preparation of the target compounds possessing phenolic groups is also illustrated in Scheme I. The *O*-benzyl ether derivatives **19** and **20** were obtained as the hydrochloride salts on treatment of the isomeric chloroquinazoline **15** and **17** with the appropriate β-arylethanolamine (**10**, **12**, or **13**) in a sealed reaction vessel at elevated temperature. The specific reaction conditions employed and physical properties of **19** and **20** are provided in Table I. Catalytic hydrogenolysis of **15** and **17** provided the desired phenolic derivatives, **6** and **7**. Analytical data of all the quinzaoline salts obtained are consistent with existence of the compounds as the monohydrochloride salts.

Initial attempts to effect hydrogenolysis of **19** and **20** involved hydrogenation of a methanolic solution of the *O*-benzyl derivative, as the hydrochloride salt, over 5% palladium-on-charcoal in the presence of a small amount of hydrochloric acid. This resulted in the isolation of dark byproducts and, in one case, resulted in hydrolysis to the corresponding 4-quinazolinone derivative. Although the results were greatly improved by omitting the hydrochloric acid from the hydrogenation mixture, the phenolic products still proved difficult to purify. Indeed the resorcinol derivative **7d** was never obtained in sufficient purity to permit pharmacological evaluation. The physical properties of the remaining phenolic derivatives of **6** and **7** are provided in Table II.

Results and Discussion

The target compounds of this study were evaluated for their ability to relax tracheal smooth muscle and for their ability to inhibit bovine heart phosphodiesterase. Theophylline was chosen as a standard for comparison in these studies because of its reported activity as both smooth muscle relaxant and phosphodiesterase inhibitor as well

Scheme I



c, Ar = 3-OH-C_6H_4; d, Ar = 3,5-$(OH)_2$-C_6H_3; e, Ar = 3-CH_2OH-4-OH-C_6H_3

as its usefulness as a bronchodilator in the clinical setting. The results of these studies are provided in Table III. Tracheal smooth muscle relaxation was determined in a manner similar to that of Fredholm and co-workers using tracheal preparations contracted to approximately 50% of their maximal contraction.[19] Whenever possible, potencies of the test compounds were expressed as the ED_{50}, that concentration required to produce 50% of the maximal papaverine-induced relaxation. In a number of instances, the maximum relaxation produced by the test compounds was less than 50% of the maximal papaverine-induced relaxation. In these cases, the maximum relaxation observed with the compounds is reported (Table III). The most potent tracheal smooth muscle relaxant among the test compounds is the resorcinol derivative **6d**, which is significantly more potent than the standard theophylline. The slopes of the log dose–response curves generated for **6b** and **7e** are significantly different from that for theophylline. This would suggest that the mechanism by which these compounds produce tracheal smooth muscle relaxation is different from that of theophylline.

Inhibition of bovine heart phosphodiesterase was determined by using the method of Butcher and Sutherland.[20] This procedure couples the phosphodiesterase-catalyzed conversion of cyclic AMP to 5′-AMP with the 5′-nucleotidase-catalyzed hydrolysis of 5′-AMP. Phosphodiesterase activity may therefore be determined by measurement of the inorganic phosphate produced in the presence of an excess of 5′-nucleotidase. While this assay is less sensitive than radioisotopic phosphodiesterase assays and likely underestimates the relative inhibitory potencies of the test compounds, the results of this evaluation indicate that the quinazoline derivatives are significantly more potent than theophylline as inhibitors of phosphodiesterase. The most potent enzyme inhibitors are the quinazoline derivatives having the simplest β-arylethylamine moieties at the 2- and 4-positions, **6a** and **7a**, respectively.

The lack of a correlation between tracheal smooth muscle relaxation and phosphodiesterase inhibition would suggest that the test compounds produce smooth muscle relaxation by an alternate mechanism. Indeed there is considerable controversy in the literature regarding the role of phosphodiesterase inhibition in the bronchodilatory activity of theophylline.[21-23] Examination of the effect

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of the test compounds on the kinetics of the enzymatic reaction reveals varying modes of inhibition, as determined by double-reciprocal plots. This, coupled with the differences observed in the slope of the log dose–relaxation curves, suggests that the test compounds, although very similar structurally, produce their pharmacological effects via diverse mechanisms.

Experimental Section

Synthetic Methodology. All melting points were taken on an Mel-Temp apparatus and are corrected. Infrared spectra were obtained with a Perkin-Elmer 281B, a Perkin-Elmer Model 257, or a Beckman IR-33 infrared spectrometer. All ^1H NMR spectra were obtained on a JEOLCO C-60-HL or a Varian EM-390 spectrometer and values are reported in ppm (δ) from Me_4Si. ^{13}C NMR spectra were obtained on a JEOL FX-60 Fourier transform spectrometer and values are reported in ppm from Me_4Si. Thin-layer chromatography was performed on Macherey-Nagel glass plates precoated with silica gel G (0.25 mm) with fluorescent indicator. Mass spectra were obtained at an electron energy of 70 eV on a Finnegan Model 3200 gas chromatograph/mass spectrometer/data system instrument. The term "in vacuo" refers to water aspirator vacuum. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN, Atlantic Microlab, Atlanta, GA, or M-H-W Laboratories, Phoenix, AZ. All compounds prepared exhibited IR, ^1H NMR, and mass spectral characteristics that were consistent with the assigned structure.

Ethyl 5-Acetyl-2-(benzyloxy)benzoate (8). To a solution of ethyl 5-acetylsalicylate[24] (10.4 g, 50 mmol) and benzyl chloride (7.0 g, 55 mmol) in 20 mL of Me_2SO was added anhydrous K_2CO_3 (11.0 g, 55 mmol). The resulting suspension was stirred with an overhead stirrer and heated in a 75 °C oil bath for 5 h. The cooled suspension was diluted with Et_2O and filtered, and the collected solids were washed with Et_2O. The filtrate was washed with H_2O and the aqueous layer extracted with Et_2O (2 × 150 mL). The combined Et_2O extracts were dried (Na_2SO_4) and concentrated in vacuo, and the residual cream-colored solid recrystallized from hexane to yield 11.1 g (74%) of white needles: mp 78–79 °C. Anal. ($C_{18}H_{18}O_4$) C, H.

Ethyl 2-(Benzyloxy)-5-(2-bromoacetyl)benzoate (9). A suspension of 8 (10.0 g, 33.5 mmol) and anhydrous K_2CO_3 (4.7 g, 34 mmol) in 200 mL of $CHCl_3$ was stirred in an ice bath as a solution of Br_2 (5.4 g, 34 mmol) in 140 mL of $CHCl_3$ was added dropwise over a period of 3 h. The reaction mixture was filtered, the solids were washed with $CHCl_3$, and the filtrate was concentrated in vacuo. Elution of the residual orange solid through a short silica gel 60 (70–270 mesh ASTM, Macherey-Nagel) column with $CHCl_3$ followed by recrystallization from cyclohexane afforded 9.5 g (75%) of a while solid: mp 116.5–117.5 °C. Anal. ($C_{18}H_{17}BrO_4$) C, H.

α^1-(Aminomethyl)-4-(benzyloxy)-1,3-benzenedimethanol (10). A solution of NaN_3 (2.3 g, 35 mmol) in 25 mL of H_2O was added dropwise to a warm stirred solution of **9** (10.9 g, 29 mmol) in 75 mL of Me_2CO. The cooled white suspension was refrigerated several hours and then filtered to yield 9.1 g (93%) of the α-azido ketone as a white crystalline solid: mp 104–105 °C. A solution of the azido ketone (9.1 g) in 300 mL of anhydrous THF was added slowly to a stirred suspension of $LiAlH_4$ (2.0 g) in 200 mL of anhydrous THF and the resulting suspension heated at reflux temperature for 3 h under N_2. Excess $LiAlH_4$ in the cooled reaction mixture was decomposed by the addition of $Na_2SO_4 \cdot 10H_2O$. The suspension was filtered, the solids were washed with THF, and the filtrate was concentrated in vacuo. The residual off-white solid was recrystallized from CH_3CN to yield 5.7 g (78%) of a cream-colored crystalline solid: mp 143–144 °C. Anal. ($C_{16}H_{19}NO_3$) C, H, N.

3,5-Bis(benzyloxy)benzaldehyde (11). A solution of 3,5-bis(benzyloxy)benzyl alcohol (10.0 g, 31.2 mmol) in 30 mL of CH_2Cl_2 was added to a suspension of pyridinium chlorochromate (10.0 g, 46.8 mmol) in 30 mL of CH_2Cl_2 and the dark reaction mixture stirred at room temperature for 1 h. The mixture was diluted with 150 mL of Et_2O and filtered, and the filtrate was dried (K_2CO_3). Concentration in vacuo afforded a green solid, which was eluted (C_6H_6) through a short column of silica gel 60 (70–270 mesh ASTM, Macherey-Nagel) to give 9.1 g (91%) of a white crystalline solid: mp 77.5–79 °C (lit.[25] mp 80 °C).

α-(Aminomethyl)-3,5-bis(benzyloxy)benzyl Alcohol (12). A mixture of 11 (8.3 g, 26.1 mmol) and a catalytic amount of anhydrous ZnI_2 was placed in a cool, flame-dried flask and the solid mixture maintained under a blanket of N_2. Me_3SiCN (5.0 mL, 3.7 g, 37 mmol) was added slowly via syringe and the mixture stirred at room temperature until it became an orange oil: IR (neat) 2190 (CN) cm^{-1}. The crude oil was dissolved in 100 mL of anhydrous THF and added dropwise to a suspension of $LiAlH_4$ (1.4 g) in 150 mL of anhydrous THF. After the resulting green suspension was refluxed for 3 h, excess $LiAlH_4$ in the cooled reaction mixture was decomposed by successive dropwise addition of 2 mL of H_2O, 2 mL of 15% NaOH, and 6 mL of H_2O. The suspension was filtered, the solids were washed several times with THF, and the filtrate was dried (K_2CO_3). Removal of solvent in vacuo afforded an orange oil, which was recrystallized from C_6H_6/petroleum ether to give 7.5 g (82%) of a white solid: mp 92–94 °C. Anal. ($C_{22}H_{23}NO_3$) C, H, N.

2-Chloro-4-(diethylamino)-6,7-dimethoxyquinazoline (15). To a solution of 2,4-dichloro-6,7-dimethoxyquinazoline (14; 1.0 g, 3.8 mmol) in 50 mL of anhydrous THF was added $HNEt_2$ (0.9 mL, 0.6 g, 8.7 mmol). Within 10 min $HNEt_2 \cdot HCl$ began precipitating out of the reaction mixture. After stirring for 16 h at room temperature, the mixture was filtered and the filtrate concentrated in vacuo to give 1.0 g (87%) of a pale yellow solid: mp 145.5–148 °C. A small amount of this material was purified for elemental analysis by flash chromatography (silica gel 60, 230–400 mesh ASTM, E. Merck) with EtOAc/petroleum ether (1:2) as elution solvent, providing a white crystalline solid: mp 148.5–149 °C. Anal. ($C_{14}H_{18}ClN_3O_2$) C, H, N.

4-(Diethylamino)-6,7-dimethoxy-2-[(2-phenylethyl)amino]quinazoline (6a). A mixt of 15 (630 mg, 2.1 mmol) and phenethylamine (0.6 mL, 0.6 g, 4.7 mmol) in 15 mL of absolute EtOH was heated at 130 °C for 12 h in a sealed metal reaction vessel. After the mixture cooled to room temperature, the solvent was removed in vacuo. The resulting dark solid was slurried in Et_2O for 3 h, filtered, washed with H_2O, and recrystallized from EtOH/H_2O to give 350 mg (44%) of off-white needles: mp 116–117 °C. Anal. ($C_{22}H_{28}N_4O_2$) C, H, N.

A small amount of **6a** was dissolved in THF and a saturated solution of HCl in anhydrous THF added dropwise. The solvent was removed in vacuo to provide **6a**·HCl as a white solid: mp 197–198.5 °C.

4-(Diethylamino)-6,7-dimethoxy-2-[(2-hydroxy-2-phenylethyl)amino]quinazoline (6b). A mixture of 15 (2.0 g, 6.6 mmol) and 2-amino-1-phenylethanol (1.9 g, 13.8 mmol) in 15 mL of absolute EtOH was flushed with N_2 and then heated at 120 °C in a sealed metal reaction vessel for 12 h. The cooled solution was concentrated in vacuo and the residual yellow solid slurried in H_2O for 2 h. Crystallization of the filtered solid from aqueous EtOH afforded 2.1 g (81%) of pale yellow crystals: mp 155–156.5 °C. Anal. ($C_{22}H_{28}N_4O_3$) C, H, N.

A small amount of the material was heated in 10% HCl for 30 min and the cooled mixture refrigerated overnight. Filtration afforded **6b**·HCl as a white solid: mp 223.5–225 °C.

2-Chloro-4-[(2-phenylethyl)amino]-6,7-dimethoxyquinazoline (18). To a solution of 14 (10.0 g, 39 mmol) in 500 mL of THF was added phenethylamine (10.0 mL, 9.6 g, 79 mmol). The reaction mixture was stirred at room temperature for 24 h and filtered, and the filtrate concentrated in vacuo. The resulting yellow oil was stirred in petroleum ether overnight, giving a white solid which was recrystallized from MeOH to give 12.2 g (92%) of white prisms: mp 150–152 °C. Anal. ($C_{18}H_{18}ClN_3O_2$) C, H, N.

2-(Diethylamino)-6,7-dimethoxy-4-[(2-phenylethyl)amino]quinazoline (7a). A mixture of 18 (1.0 g, 2.9 mmol) in 10 mL of $HNEt_2$ was heated in a sealed glass-lined metal reaction vessel at 145 °C for 12 h. After the mixture cooled to room temperature, excess $HNEt_2$ was removed in vacuo. The resulting

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dark solid was dissolved in aqueous EtOH, decolorized with activated charcoal, and recrystallized from aqueous EtOH to give 475 mg (43%) of white needles: mp 180.5–181 °C. Anal. ($C_{22}H_{28}N_4O_2$) C, H, N.

A small amount of **7a** was dissolved in anhydrous THF and a saturated solution of HCl in anhydrous THF added dropwise. Concentration in vacuo provided **7a**·HCl as a white solid: mp 204–205 °C.

2-(Diethylamino)-6,7-dimethoxy-4(3*H*)-quinazolinone (16). A mixture of **14** (7.5 g, 29 mmol) in 175 mL of 1 N NaOH and 50 mL of THF was stirred for 8 h at room temperature under a N_2 atmosphere. The reaction mixture was then stirred in an ice bath for 30 min and acidified to pH 5 with HOAc. The yellow precipitate was filtered, dried, and used without further purification. A mixture of the precipitate and $HNEt_2$ (11 mL) in 25 mL of absolute EtOH was heated in a N_2-purged pressure bottle at 130 °C for 6 h. The yellow solution was cooled in an ice bath and filtered to give 6.7 g (83%) of dense cream-colored crystals: mp 216–218 °C (lit.[17] mp 216–217 °C).

4-Chloro-2-(diethylamino)-6,7-dimethoxyquinazoline (17). A solution of **16** (14.3 g, 51.6 mmol) in 90 mL of $POCl_3$ was stirred while *N,N*-dimethylaniline (15 mL) was added over a period of 30 min. After the resulting yellow solution was refluxed for 90 min, the cooled reaction mixture was concentrated in vacuo and the residual orange semisolid added to 500 mL of ice–25% NaOH. The resulting suspension was extracted with CH_2Cl_2 (3 × 350 mL), and the combined organic extracts were washed with brine (2 × 350 mL) and dried (K_2CO_3). Removal of solvent in vacuo afforded a green solid which was recrystallized from MeOH to give 12.9 g (85%) of pale yellow needles: mp 130–131 °C (lit.[26] mp 129–131 °C).

2-(Diethylamino)-6,7-dimethoxy-4-[(2-hydroxy-2-phenylethyl)amino]quinazoline (7b). A solution of **17** (1.3 g, 4.4 mmol) and 2-amino-1-phenylethanol (2.6 g, 19 mmol) in 100 mL of anhydrous THF was heated at reflux temperature for 90 h. The solution was concentrated in vacuo and the residual oil slurried in H_2O. The resulting suspension was filtered and the solid recrystallized from EtOAc to provide 1.1 g (63%) of a white solid: mp 219–221 °C. Anal. ($C_{22}H_{28}N_4O_3$) C, H, N.

General Procedure for Preparation of 19 and 20. A mixture of the halogenated quinazoline (**15** or **17**, 3.3 mmol) and the appropriate primary amine (**10**, **12**, or **13**, 3.7 mmol) in 25 mL of absolute EtOH was sealed in a glass-lined N_2-purged metal reaction vessel and the vessel heated in an oil bath at 100–130 °C until the reaction appeared complete by TLC. The product was collected from the cooled reaction mixture either by filtration or concentration in vacuo and purified by recrystallization.

General Procedure for Catalytic Hydrogenolysis. A solution of the appropriate *O*-benzyl derivative (**19** or **20**, 1 mmol) in MeOH was hydrogenated over 5% Pd–C in a Paar hydrogenator until the reaction appeared complete by TLC. The reaction mixture was filtered through Celite, the filtrate concentrated in vacuo, and the residue purified by recrystallization.

Pharmacological Methodology. Tracheal Smooth Muscle Relaxation. Tissue preparation was similar to that described by Constantine.[27] A female Hartley guinea pig (300–500 g) was sacrificed by a blow to the head and the trachea rapidly excised, cut in a spiral fashion, and mounted in a jacketed organ bath of the overflow type containing Krebs–Henseleit solution continuously aerated with 95% O_2/5% CO_2 and maintained at 37 °C.

The tissue was adjusted to an initial tension of 1.5 g and allowed to equilibrate 1 h. Pilocarpine hydrochloride was added to the bath in a cumulative manner until maximal contraction of the tissue was achieved. The tissue was then relaxed by the addition of papaverine hydrochloride (10 μg/mL). The bath was flushed several times with fresh buffer after which the smooth muscle tone was increased to approximately 50% of the maximal contraction by the addition of pilocarpine. After the tension had stabilized, cumulative doses of the test compound, as the hydrochloride salt, were added. At the conclusion of the experiment, a supramaximal dose (10 μg/mL) of papaverine was added to the medium. The relaxation produced by each dose of the test compound was expressed as a percentage of the maximal papaverine-induced relaxation. For each compound producing greater than 50% of the maximal papaverine-induced relaxation, a composite log dose–response curve was obtained by combining data from four to six tissues. The ED_{50}, the concentration required to produce 50% of the maximal papaverine-induced relaxation, was obtained from the composite log dose–response curve. Confidence limits of the ED_{50} and analysis for parallelism of the curves was determined by the method of Goldstein.[28]

Stock solutions of pilocarpine hydrochloride and papaverine hydrochloride were prepared in distilled water. Theophylline was dissolved in distilled water containing 1 equiv of 0.5 N NaOH. Whenever possible, stock solutions of the test compounds were prepared with distilled water as the solvent. In some cases, however, it was necessary to use aqueous EtOH or aqueous Me_2SO to prepare the stock solutions. Final bath concentrations of EtOH never exceeded 1%, while final Me_2SO concentrations in the organ bath did not exceed 0.05%. Control experiments were conducted and whenever necessary the results obtained with the test compounds were adjusted to correct for the effects of the vehicle.

Phosphodiesterase Inhibition. Enzyme activity was determined by measuring the production of inorganic phosphate in the presence of an excess of 5′-nucleotidase. Each sample contained 1 mM cyclic AMP (Sigma), 3 mM $MgSO_4$, 0.02 unit of bovine heart phosphodiesterase (Sigma P 0134), 0.02 unit of 5′-nucleotidase (Sigma), the appropriate concentration of test compound in water, and Tris-HCl buffer, pH 7.5 (50 mM), in a final volume of 1 mL. The reagents were mixed in incubation vessels, and the reaction was initiated by the addition of the cyclic AMP and allowed to proceed for 20 min in a 30 °C water bath. The reaction was terminated by addition of 0.2 mL of 5% trichloroacetic acid. The following reagents were added: 0.4 mL of acid molybdate reagent, 0.4 mL of Elon reducing agent, 1.0 mL of H_2O to give a final volume of 3.0 mL. The solutions were vortexed and then centrifuged at 800*g* for 10 min. Color was allowed to develop for 20 min, and the absorbance at 660 nm was determined. The quantity of inorganic phosphate was determined from a standard curve and reported as micromoles of PO_4/20 min of reaction time.

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Registry No. **6a**, 92900-80-6; **6a**·HCl, 92900-81-7; **6b**, 92900-82-8; **6b**·HCl, 92901-03-6; **6c**·HCl, 92900-83-9; **6c**, 92900-84-0; **6d**·HCl, 92900-86-2; **6d**, 92900-85-1; **6e**·HCl, 92900-87-3; **6e**, 92900-88-4; **7a**, 92900-89-5; **7a**·HCl, 92900-90-8; **7b**, 92900-91-9; **7c**·HCl, 92900-92-0; **7c**, 92900-93-1; **7e**·HCl, 92900-94-2; **7e**, 92900-95-3; **8**, 60561-28-6; **9**, 56443-71-1; **10**, 92900-77-1; **11**, 14615-72-6; **12**, 41852-55-5; **13**, 62932-74-5; **14**, 27631-29-4; **15**, 92900-78-2; **16**, 16175-94-3; **17**, 23673-07-6; **18**, 92900-79-3; **19a**, 92900-96-4; **19b**, 92900-97-5; **19c**, 92900-98-6; **20a**, 92900-99-7; **20b**, 92901-00-3; **20c**, 92901-01-4; ethyl 5-acetylsalicylate, 16475-93-7; α-azido ketone, 92901-02-5; 3,5-bis(benzyloxy)benzyl alcohol, 24131-31-5; diethylamine hydrochloride, 660-68-4; phenethylamine, 64-04-0; 2-amino-1-phenylethanol, 7568-93-6; cAMP phosphodiesterase, 9036-21-9; benzyl chloride, 100-44-7.

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