Journal of Medicinal Chemistry

Volume 18, Number 5 May 1975

Synthesis and Biological Evaluation of Some 10-Substituted 2,3-Dihydroimidazo[2,1-*b*]quinazolin-5(10*H*)-ones, a New Class of Bronchodilators†

Goetz E. Hardtmann,* Gabor Koletar, Oskar R. Pfister,

Medicinal Chemistry Department

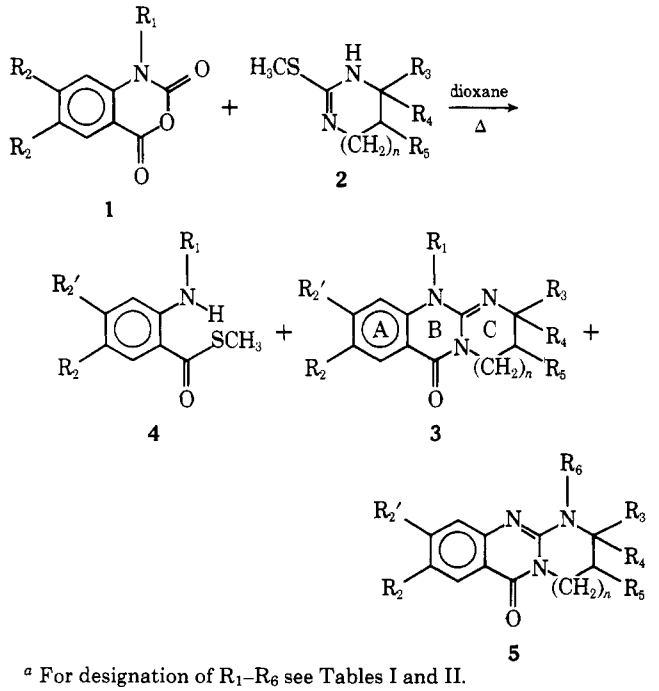
John H. Gogerty,* and Louis C. Iorio

Biology Department, Sandoz, Inc., Pharmaceutical Division, East Hanover, New Jersey 07936. *Received October 15, 1974*

On treatment of N-substituted isatoic anhydrides with 2-methylmercaptoimidazolines, 10-substituted imidazo[2,1-*b*]quinazolin-5(10*H*)-ones are obtained. Several members of this class exhibited pronounced broncholytic activity. The structure–activity relationships (based on results obtained in the guinea pig histamine aerosol test) of these non-sympathomimetic bronchodilators are discussed. In addition, the detailed pharmacological evaluation of two analogs found to be five to ten times more active than theophylline as bronchodilators without having central nervous system or cardiovascular side effects is described.

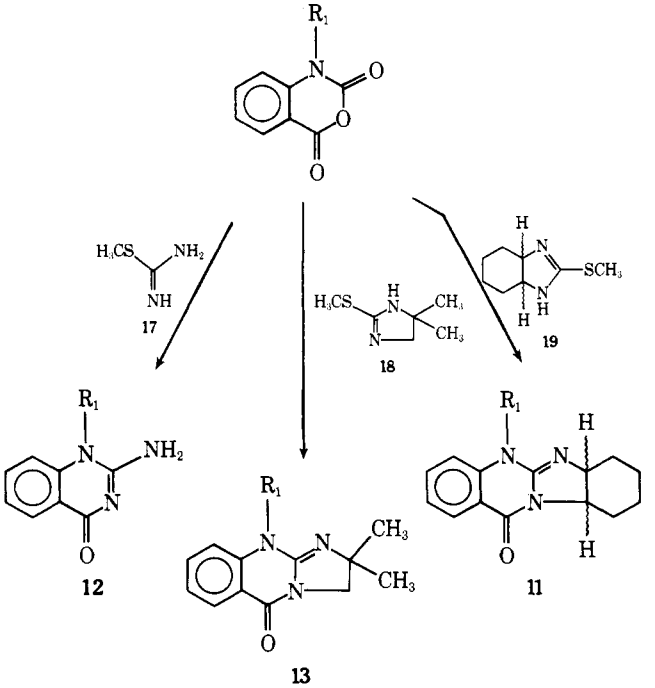
As part of our investigation into the chemistry of isatoic anhydrides[1] (**1**), we studied the reaction with *S*-alkylthioureas (e.g., **2**). As previously described[2-4] this reaction proceeds readily at 100° in dioxane or other inert solvents (Scheme I). When *N*-alkylisatoic anhydrides[1a] (**1**, R_1 = alkyl) were allowed to react with 2-methylmercaptoimidazolines, compounds of type **3** and minor amounts of *S*-methyl esters of thioanthranilic acid (**4**)[3] were formed. Analogously N-unsubstituted isatoic anhydrides lead to products of type **5** (R_6 = H), which may be alkylated at N-1 (R_6 = H to R_6 = alkyl) by standard procedures. The use of some other thioureas in the reaction with isatoic anhydride is illustrated in Scheme II.

Scheme I[a]



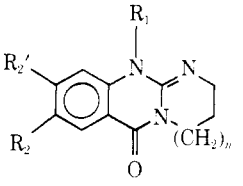
[a] For designation of R_1–R_6 see Tables I and II.

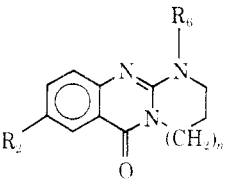
Scheme II



† Presented in part before the Division of Medicinal Chemistry Section of the 168th National Meeting of the American Chemical Society, Atlantic City, N.J., Sept 1974.

Table I


type A


type B

No.	Type	n	R_1	R_2	R_2'	R_6	Yield, %	Mp, °C	Solvent	Analyses	% protection[c] at 60 mg/kg
20	B	0		H	H	H	52	262–264	MeOH	C, H, N	20
21	A	0	Methyl	H	H		50	213–215	EtOAc	N, O	20
22	A	0	Methyl	Cl	H		60	200–202	CH_2Cl_2	C, H, N	60
23	A	1	Methyl	Cl	H		38	119–120	EtOAc	C, H, N	Weak[d]
24	A	2	Methyl	Cl	H		22	118–119	Et_2O	C, H, N	Weak
25	A	0	Ethyl	H	H		42	150–152	CH_2Cl_2	C, H, N	60
26	A	0	Ethyl	Cl	H		50	155–157	Et_2O	C, H, N	40
27	A	0	Methyl	H	Cl		63	227–279	EtOH	C, H, N	40
28	B[a]	1		Cl	H	Methyl	68	114–116	Et_2O	C, H, N	20
29	B[a]	1		H	Cl	Ethyl	67	129–131	Et_2O	C, H, N	Weak
30	A	0	Isopropyl	H	H		60	149–151	Et_2O	C, H, N	75
31	A	0	Methyl	OMe	OMe		49	253–256	$CHCl_3$	C, H, N	40
32	A	0	Allyl	H	H		36	119–121	CH_2Cl_2[b]	C, H	Weak
33	A	0	2-Butenyl	H	H		38	100–102	CH_2Cl_2	C, H, N	50
34	A	0	3-Butenyl	H	H		40	96–98	Et_2O	C, H, N	40
35	A	0	Propargyl	H	H		42	190–192	CH_2Cl_2[b]	C, H	Weak
36	A	0	5-Hexenyl	H	H		30	59–62	Et_2O	C, N, H	60
37	A	0	Cyclopropylmethyl	H	H		47	125–128	Pentane	C, H, N	Weak
38	A	0	Cyclohexylmethyl	H	H		32	142–144	Et_2O	C, H, N	Weak
39	A	0	Phenyl	H	H		46	297–299	MeOH	C, H, N	Weak
40	A	1	Phenyl	H	H		41	229–231	EtOAc	C, H, N	Weak
41	A	0	Cyclohexyl	H	H		56	196–198	Et_2O	C, H, N	Weak
42	A	0	n-Hexyl	H	H		33	79–81	Et_2O	C, H, N	Weak
43	A	0	Cyanomethyl	H	H		54	93–95	CH_2Cl_2[b]	C, H, N	100
44	A	0	Benzyl	H	H		55	203–205	CH_2Cl_2	C, H, N	100
45	B[a]	0		H	H	Benzyl	80	118–120	Et_2O	C, H, N	Weak
46	A	0	2-Furfuryl	H	H		39	150–153	CH_2Cl_2[b]	C, H, N	25
47	A	0	2-Thenyl	H	H		19	124–127	CH_2Cl_2[b]	C, H, N	50
Theophylline											50

[a] Prepared by procedure B. [b] Crystallization in the presence of diethyl ether. [c] See ref 5. [d] Weak: less than 20% protection at 60 mg/kg.

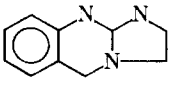
The general pharmacological evaluation of the initial prototypes (compounds of type **3** and **5**) prepared in this series revealed moderate mixed CNS and hypotensive activity for those of type **3** (e.g., 22) and moderate antiinflammatory activity for the compounds of type **5** (R_6 = alkyl). These observations led to a broad synthetic program and extensive biological testing. During the course of this study it was discovered that 2,3-dihydro-10-ethylimidazo[2,1-*b*]quinazolin-5(10*H*)-one (**25**) on oral administration protected the guinea pig against histamine-induced bronchospasm, at a dose similar to that found with theophylline. Further biological investigation revealed that the compound was free of the CNS and cardiovascular effects usually associated with theophylline-like compounds and did not exert its effect through an action on β-adrenergic receptors.

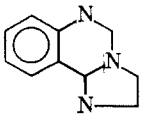
This publication will report our efforts to find compounds (Tables I and II) with greater potency than **25** and a discussion of their biological evaluation.

Synthesis. The required N-substituted isatoic anhydrides[1a] are readily prepared either by alkylation of the unsubstituted precursors (**1**, R_1 = H) or by acylation of N-substituted anthranilic acids with phosgene in the presence of base. (A detailed discussion of these preparations will be published elsewhere.)[1b]

The preparations of the hydroiodides of the methylmercaptoureas (e.g., **2**) by the reaction of diamino precursors with carbon disulfide followed by alkylation with methyl iodide proceeded unexceptionally and are described in the Experimental Section. In some cases the bases of these products were unstable and difficult to isolate and we preferred to liberate those from the hydroiodides in situ (by adding an excess of potassium or sodium carbonate). Compounds of type **5** in which R_6 = alkyl or benzyl were prepared by alkylation of the sodium salt of **5** (R_6 = Na). Alkylation occurs exclusively in ring C as indicated by the distinctly different uv spectrum [for compound **28**, λ max 228 mμ (ϵ 31,200), 280 (23,700), 349 (3300)] when compared with the analogous ring B alkyl isomers [for compound **23**, λ max 232 mμ (ϵ 25,300), 254 (21,900), 355 (1900)].

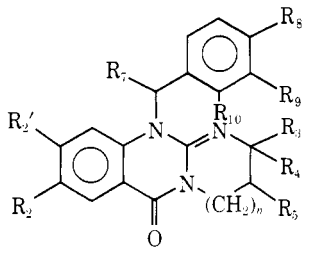
From the viewpoint of structure–activity relationship it became interesting to prepare the [1,2-*c*] analog **10** of one


[2,1-*b*]


[1,2-*c*]

of our most active derivatives. The synthesis is shown in Scheme III. For comparative purposes we also prepared

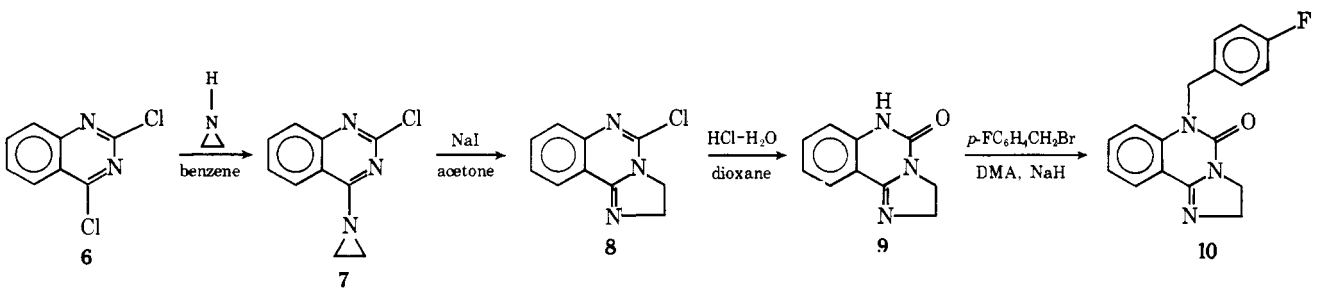
Table II



No.	n	R_2	R_2'	R_3	R_4	R_5	R_7	R_8	R_9	R_{10}	Yield, %	Mp, °C	Solvent	Analyses	% protection[d] at 60 mg/kg	ED_{50}
44	0	H	H	H	H	H	H	H	H	H					100	17.5
48	0	H	H	H	H	H	Me	H	H	H	62	136–138	Et_2O	C, H, N	75	43
49	0	H	H	H	H	H	Ph	H	H	H	16	208–212	CH_2Cl_2	C, H, N	Weak[e]	
50	1	H	H	H	H	H	H	H	H	H	11	158–160	CH_2Cl_2	C, H, N	80	17
51	2	H	H	H	H	H	H	H	H	H	25	103–105	Et_2O	C, H, N	40	
52	0	H	H	H	H	H	H	Me	H	H	51	197–198	MeOH	C, H, N	Weak	
53[g]	0	H	H	H	H	H	H	H	H	Me	62	211–213	CH_2Cl_2	C, H, N	80	30
54	0	H	H	H	H	H	H	OMe	OMe	H	42	181–183	MeOH	C, H, N	20	
55	1	H	H	H	H	H	H	OMe	OMe	H	35	142–144	Et_2O	C, H, N	40	
56	0	OMe	OMe	H	H	H	H	H	H	H	41	187–189	EtOAc	C, H, N	Weak	
57	0	OMe	H	H	H	H	H	H	H	H	64	173–175	MeOH	C, H, N	20	
58	0	Cl	H	H	H	H	H	H	H	H	64	189–191	CH_2Cl_2	C, H, N	20	
59[g]	0	H	Cl	H	H	H	H	H	H	H	65	190–191	CH_2Cl_2	C, H, N	20	
60	0	H	H	H	H	H	H	Cl	H	H	55	225–227	CH_2Cl_2	C, H, N	60	6.5
61	1	H	H	H	H	H	H	Cl	H	H	14	178–180	CH_2Cl_2[b]	C, H, N	75	27.5
62	0	H	H	H	H	H	H	Br	H	H	46	175–177	CH_2Cl_2[b]	C, H, N	90	13.7
14	0	H	H	H	H	H	H	F	H	H	65	192–194	MeOH	C, H, N	100	3.5
64	0	H	Cl	H	H	H	H	F	H	H	35	174–176	CH_2Cl_2[b]	C, H, N	40	
65[f]	0	H	H	H	H	H	H	H	F	H	53	212–215	MeOH	C, H, N	50	60
66[f]	0	H	H	H	H	H	H	H	H	F	40	213–215	MeOH	C, H, N	50	60
67	1	H	H	H	H	H	H	F	H	H	21	154–156	Et_2O	C, H, N	100	11
68	0	H	H	H	H	H	H	F	F	H	46	209–211	MeOH	C, H	60	51
69	0	H	H	Me[c]	H	H	H	F	H	H	43	122–125	CH_2Cl_2	C, H, N	100	30
70	0	H	H	Me[c]	Me[c]	H	H	F	H	H	21	114–118	CH_2Cl_2[b]	C, H, N	100	25
71	0	H	H	H	$CH_2(CH_2)_2CH_2$		H	F	H	H	25	196–199	CH_2Cl_2	C, H	100	25
72[f]	0	H	H	H	Me	Me	H	F	H	H	36	245	CH_2Cl_2	C, H	80	27
73	0	H	H	H	H	H	H	H	CF_3	H	44	141–143	CH_2Cl_2	C, H	Weak	
74	0	H	H	H	H	H	H	H	H	NO_2	35	266–268	EtOH	C, H, N	Weak	
75[g]	2,3-Dihydro-10-(β-phenylethyl)imidazo[2,1-*b*]quinazolin-10(5*H*)-one										71	166–168	MeOH	C, H, N	20	
16	2,3-Dihydro-10-(*p*-fluorobenzyl)imidazo[2,1-*b*]quinazoline-10(5*H*)-thione										57	222–224	CH_2Cl_2	C, H	80	22.5
15	10-(*p*-Fluorobenzyl)imidazo[2,1-*b*]quinazolin-10(5*H*)-one										32	157–159	CH_2Cl_2	C, H, N	100	15
12	2-Amino-1-(*p*-fluorobenzyl)quinazolin-4(1*H*)-one hydrogen maleate										21	207–210	EtOH	C, H, N	100	18
10	2,3-Dihydro-6-(*p*-fluorobenzyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one										72	148–150	CH_2Cl_2	C, H, N	20[a]	
Theophylline															50	

[a] Tested at 30 mg/kg. [b] Crystallized in the presence of diethyl ether. [c] The positions of the methyl groups have been assigned only tentatively. [d] See ref 5. [e] Weak: less than 20% protection at this dose. [f] Characterized and tested as hydrochlorides. [g] Tested as methanesulfonates.

Scheme III



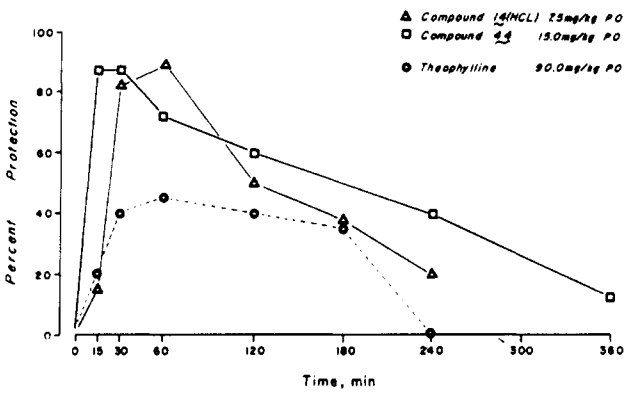
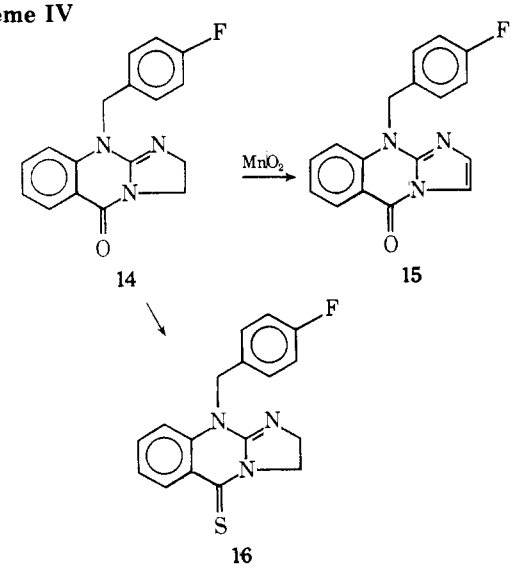


Figure 1. Onset and duration of protective activity against histamine aerosol induced bronchoconstriction after oral administration of compound **14** HCl (△), compound **44** (□), and theophylline (○).

Scheme IV



some thione analogs (e.g., **16**) and the unsaturated compound **15** (Scheme IV). Representative preparative procedures are listed in the Experimental Section.

Pharmacology. A modification of the technique of Van Arman et al.[5] was used as the primary screen for all reported compounds. Conscious female Hartley guinea pigs (180–220 g) were fasted for 12 hr, dosed orally, and challenged with histamine aerosol (0.2% aqueous solution of histamine in a Vaponephrin Pocket Nebulizer) sprayed into a closed transparent cage at 10 lb/in.^{2} pressure. The respiratory status reflecting the increasing degrees of bronchoconstriction was observed. Control animals became unconscious 80 ± 6 sec after the spray was introduced. Animals remaining conscious for more than 120 sec were considered protected against histamine-induced bronchospasm.

Theophylline, which provides protection against histamine-induced bronchospasm in 50% of the animals at 60 mg/kg orally, was used as the standard agent.

Those compounds that were found to be significantly more active than the reference substance as bronchodilators (i.e., **44** and **14**) were submitted to tests in which duration of action and development of tolerance could be examined. In addition, the relaxant effects on bronchial smooth muscle were investigated utilizing the microshock anaphylaxis technique described by Van Arman et al.[5] and using isolated guinea pig tracheal strips prepared according to the method of Constantine.[6] Other pharmacological tests were carried out in order to compare the specificity of

Table III. Protective Effects of 14 HCl, 44, and Theophylline against Egg Albumin Induced Anaphylaxis (Microshock) in Guinea Pigs. Effects Were Determined 1 Hr after Oral Administration

Treatment	Dose, mg/kg po	No. of guinea pigs treated	No. of guinea pigs protected	% protection
Control		41	13	32.0
14 HCl	1.8	6	2	33.0
	3.8	6	3	50.0
	7.5	6	5	83.0
	15.0	6	5	83.0
44	30.0	10	4	40.0
	60.0	16	12	75.0
	120.0	12	11	91.6
Theophylline	7.5	8	3	38.0
	15.0	6	3	50.0
	30.0	10	7	70.0
	60.0	16	11	69.0
	120.0	12	10	83.0

bronchodilator activity for the two compounds of most interest vs. the reference substance theophylline. These additional studies included evaluation of cardiovascular effects in which male mongrel dogs weighing 11.5–16.0 kg were anesthetized with sodium pentobarbital (30 mg/kg iv). A tracheotomy was then performed to permit artificial respiration. Aortic flow was measured at the level of the aortic arch by use of a Carolina flow meter Model 322. Blood pressure was measured in the left femoral artery with a Statham P-23 pressure transducer. Heart rate was measured with standard EKG leads. All parameters were recorded by a Grass Model 7 polygraph. The drugs were administered into a femoral vein. Studies on the effects of these agents on central nervous system function included acute toxicity determinations and analysis of behavioral changes in mice according to the method defined by Irwin.[7] In addition, effects on locomotor activity in mice were analyzed using standard activity cages (darkened circular actophotometers manufactured by Woodard Research Corp., Herndon, Va.). Spontaneous activity was quantitated by counting the number of interruptions of photocell beams for 60 min starting 15 min after a group of five mice per dose was placed in the circular chamber.

The results of these more detailed pharmacological investigations indicate that **44** and **14** are approximately five and ten times more active, respectively, than theophylline as antagonists of histamine-induced bronchospasm in the guinea pig (see Figure 1). The duration of action of both substances is comparable to that of theophylline with peak effects obtained 30–60 minutes following oral administration and lasting approximately 3–4 hr. When studied in the egg albumin induced microshock test in guinea pigs, **14** appeared to be approximately four times more active than either **44** or theophylline insofar as protecting against the induced respiratory distress (Table III). The differences in relative activity of these agents in the latter test vs. the histamine aerosol test would suggest that part of the activity observed in the histamine-induced bronchospasm study could be due to antihistaminic effects. That these substances have a direct bronchial smooth muscle relaxant activity is shown by the fact that it was demonstrated that both **14** and theophylline caused concentration-dependent relaxation of spirally cut guinea pig tracheal strips. In this test, **14** appears to be approximately three times more po-

tent than theophylline. That this effect was not due to actions on β-adrenergic receptors was demonstrated by the fact that propranolol had no effect on the relaxant activity of **14** (Figure 2). Other pharmacologic effects of presently available bronchodilators contribute significant side effects in clinical use, these being primarily related to actions on the cardiovascular and central nervous systems. As shown in Table IV, **14** produces a significant reduction in blood pressure when administered intravenously to anesthetized dogs. This was found in other studies to be due to a decrease in peripheral resistance, or vasodilatation. On the other hand, aminophylline (the ethylenediamine salt of theophylline) produced a significant increase in cardiac output accompanied by a tendency toward tachycardia (increase in heart rate); **14**, on the other hand, provided no dose-related effects on cardiac function.

With regard to comparison of **14** and theophylline on central nervous system activities, Table V presents data showing that the standard produces stimulation of motor activity whereas **14** provides evidence only of central nervous system depression. These behavioral effects observed with theophylline and **14** are further supported by data obtained in actophotometer studies in mice. Here it is seen that theophylline produces significant increases in locomotor activity in mice at doses as low as 1.6 mg/kg orally whereas **14** is without effect up to doses as high as 102.4 mg/kg orally.

These data provide evidence that a novel group of chemical substances produces bronchodilator activity via a direct non-β-adrenergic relaxation of bronchial smooth muscle. In addition, at least the most active substance within the series (**14**) is devoid of those pharmacologic effects of theophylline which contribute to many of its clinical side effects (i.e., cardiac stimulation and excitation of central nervous system activity).

Structure–Activity Relations. From the percent protection data given in Table I, it is readily apparent that the maximum activity with compounds of type **3** occurs when the ring is five-membered rather than six- or seven-membered (**22** vs. **23** and **24**).

Halogen substitution in ring A had a variable influence on the activity (**22** vs. **21** and **25** vs. **26**). In the case of R_1 being alkyl, methoxy substitution in ring A had little effect, but the same substitution for R_1 = benzyl led to much lower activity (e.g., **44** vs. **54**).

A number of derivatives with alkyl substituents in ring A were prepared. In every case these variations resulted in somewhat weaker activity.

When R_1 was changed from alkyl to allyl or propargyl, the activity was greatly reduced (e.g., **25** vs. **32** or **35**). In the cases where R_1 was a long-chain alkene (e.g., **34** and **36**) moderate activity was observed. Branched alkyl group (e.g., **30**) led to active compounds whereas cycloalkylmethyl compounds (**37** and **38**) had little activity. Surprisingly the cyanomethyl derivative (**43**) had moderate to marked activity. When R_1 was phenyl no activity was observed. However, the placement of one methylene group between the nitrogen and the phenyl group resulted in markedly active compounds (**44**), but two methylene groups (**75**) led to much decreased activity. This observation led us to prepare a wide variety of *N*-benzyl derivatives which are listed in Table II.

Introduction of substituents into the benzylic methylene group had little or a slightly detrimental effect on the activity. Strongly electron-withdrawing and electron-donat-

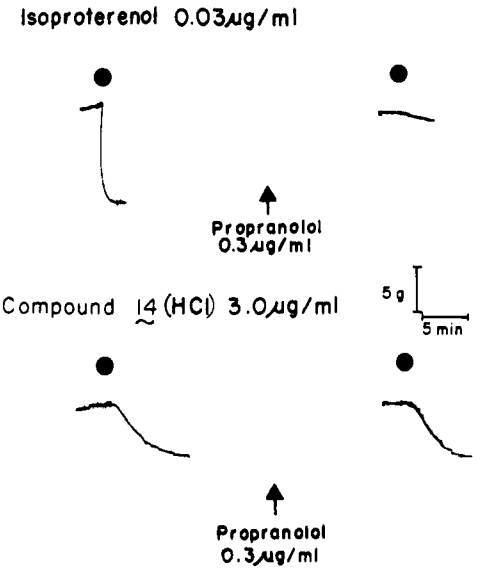


Figure 2. Effects of propranolol on compound 14 HCl and isoproterenol-induced relaxations of isolated guinea pig tracheal strips. Two different strips are shown. In both experiments, tissues were allowed to incubate in bathing medium containing propranolol, 0.3 μg/ml, for 20 min prior to obtaining the second response of the relaxant.

Table IV. Hemodynamic Effects of **14** HCl and Aminophylline in Anesthetized Dogs. Calculation Made on Results Obtained in Four Dogs with Each Drug Using the Paired t Test

		Change ± SD from controls at indicated dose (mg/kg iv) of					
		14 HCl			Aminophylline		
Parameter	Units	1	5	10	1.1	2.3	11.4
Arterial blood pressure	mmHg	−13.8 ± 3.5[a]	−34.8 ± 8.7[a]	−35.0 ± 8.2[a]	14.6 ± 10.6	14.3 ± 28.1	−17.1 ± 41.9
Heart rate	Beats/min	−5.0 ± 23.1	−8.0 ± 13.9	−14.0 ± 14.1	13.8 ± 22.4	25.5 ± 32.3	28.5 ± 29.8
LVEDP	mmHg	−1.3 ± 2.5	−2.5 ± 6.5	−1.3 ± 2.5	0.3 ± 0.5	−0.5 ± 0.8	−0.5 ± 0.5
Cardiac output	ml/min	106.3 ± 37.5[a]	31.3 ± 74.7	43.8 ± 119.7	177.5 ± 180.2[b]	235 ± 188.6[b]	340.0 ± 69.9[a]
Peripheral resistance	mmHg, min/ml	−29.0 ± 10.2[a]	−47.5 ± 17.0[a]	−49.8 ± 19.4[a]	−0.08 ± 0.55	0.43 ± 1.28	−4.5 ± 4.5
Contractile force (dp/dt)	mmHg/sec	−75.0 ± 95.7	−400.0 ± 216.0[a]	−500.0 ± 258.2	3.5 ± 3.0	6.6 ± 7.0[a]	6.5 ± 6.4[a]

[a] Significantly different from base line, $p < 0.01$. [b] Significantly different from base line, $p < 0.05$.

Table V. Acute Toxicity and Behavioral Effects of 14 HCl and Theophylline in Mice

Dose, mg/kg ip	Theophylline		14 HCl	
	No. of animals	Symptoms	No. of animals	Symptoms
800	5	Tremors, severe muscle tension, clonic/tonic convulsions (5/5 dead in 10 min)	5	Decreased spontaneous activity, ataxia, Straub tail (0.5 dead after 2 hr; 5/5 dead after 24 hr)
400	10	Same as 800 dose (10/10 dead in 2 hr)	5	Decreased spontaneous activity, ataxia, motor deficit, exopthalmos, Straub tail, tremors
200	10	Same as 400 dose (6/10 dead in 2 hr)	5	Decreased spontaneous activity, ataxia, motor deficit, docility
100	10	Ataxia, exopthalmos, hypermotility, hypersensitivity	5	Weakly decreased spontaneous activity
	LD_{50} (24 hr)[a] = 175.0 mg/kg ip		LD_{50} (24 hr)[a] = 466.6 mg/kg ip	

[a] Estimated by method of Miller and Tainter (1944).

ing groups in the phenyl ring of the benzyl moiety (e.g., CF_3 or OCH_3) reduced the activity but halogen atoms preferably in the para position had a favorable effect. Most pronounced was the activity of the *p*-fluorobenzyl derivative **14**, which was chosen for toxicological studies.

Experimental Section

All compounds gave satisfactory elemental analysis (except as noted) and their spectra (ir, Perkin-Elmer Model 137 spectrophotometer, and NMR on Varian A-60 or T-60 Models) were in full accord with the proposed structures. Melting points, obtained on a Hoover melting point apparatus, are uncorrected. Solvent evaporations were performed using a Büchi rotavapor. No attempts were made to optimize the yields in the described reactions.

***N*-(*p*-Fluorobenzyl)isatoic Anhydride (1, R_1 = *p*-Fluorobenzyl; R_2 = H). Procedure A.** Sodium hydride (5.0 g, 0.12 mol, 57% in mineral oil) was added slowly to a stirred solution of isatoic anhydride (16.3 g, 0.1 mol) in dimethylacetamide (200 ml). After the gas evolution had ceased, the mixture was allowed to stir for 30 min at room temperature. *p*-Fluorobenzyl chloride (16 g, 0.11 mol) was added and the mixture was stirred at room temperature overnight. About 50% of the solvent was evaporated in vacuo, the concentrate was poured into ice–water. The precipitate was filtered off and washed with water. The filter cake was allowed to dry and was dissolved in methylene chloride. The solution was treated with charcoal and dried over sodium sulfate. The resultant solution was evaporated and the residue crystallized from methylene chloride–ether (1:2) to obtain 14.1 g (52%) of *N*-(*p*-fluorobenzyl)isatoic anhydride (**1**, R_1 = *p*-fluorobenzyl; R_2 = H), mp 143–145°. Anal. C, H, N.

2,3-Dihydro-10-(*p*-fluorobenzyl)imidazo[2,1-*b*]quinazolin-5(10*H*)-one (14). A solution of *N*-(*p*-fluorobenzyl)isatoic anhydride (5.4 g, 0.02 mol) and 2-(methylthio)imidazoline (2.5 g, 0.022 mol) in dioxane (75 ml) was heated under reflux in the presence of one pellet of sodium hydroxide for 4 hr. The mixture was allowed to cool and was evaporated to dryness. The crystalline residue was dissolved in methylene chloride; the solution was filtered and extracted consecutively with water and twice with 1 *N* hydrochloric acid. The acidic phase was extracted once with methylene chloride, and the organic phases were discarded. The acidic solution was then neutralized with 10% sodium bicarbonate solution and the crystalline precipitate which formed was removed by filtration and washed thoroughly with water. The moist filter residue was dissolved in methylene chloride; the solution was dried over sodium sulfate, treated with charcoal, and evaporated. The residue was recrystallized from methanol to yield 3.2 g (54%) of the product (**14**), mp 192–194°. Anal. C, H, N.

1-Benzyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(10*H*)-one (45). Procedure B. To a solution of **20** (7.5 g, 0.04 mol) in dimethylacetamide (300 ml) sodium hydride (2.0 g, 0.044 mol, 57% in mineral oil) was added in small portions over a period of 15 min and the mixture was allowed to stir for 30 min at room temperature. To this mixture benzyl bromide (8.0 g, 0.046 mol) was added and the reaction mixture was allowed to remain at an ambient temperature for 15 min. The crude mixture was concentrated in vacuo (to about 150 ml) and then poured into ice–water. A crystalline precipitate formed which was filtered off, washed well with water, and dried by suction. The filter cake was dissolved in methylene chloride, dried (sodium sulfate), and treated with activated charcoal. After filtration the filtrate was evaporated and the residue crystallized from ether to obtain **45** (80%), mp 118–120°. Anal. C, H, N.

4,4-Dimethylimidazolidine-2-thione (18a). 1,2-Diamino-2-methylpropane (47 g, 0.54 mol) diluted with 55 ml of methylene chloride was added dropwise to a stirred solution of carbon disulfide (40 g, 0.53 mol) in methylene chloride (200 ml). The mixture was allowed to stir overnight. The solvent was evaporated to dryness and the residue, dissolved in 500 ml of water, was heated under reflux for 6 hr (foaming). On cooling a precipitate was formed which was removed by filtration. An additional crop could be obtained on concentration of the filtrate. The combined precipitate was collected and dried to yield **18a:** 51.1 g (73%); mp 104–107°. Anal. C, H, N.

Analogously 1,2-diaminopropane was converted into 4-methylimidazolidine-2-thione (**18b**), mp 89–93° (73%). Anal. C, H.

2-Methylthio-4,4-dimethyl-2-imidazoline (18). To a stirred suspension of 4,4-dimethylimidazolidine-2-thione (**18a**, 62.0 g, 0.48 mol) in ethanol (250 ml), methyl iodide (69 g, 0.48 mol) was added and the clear mixture was stirred for 18 hr. Three-fourths of the solvent was evaporated and the residual solution was treated with ether. On cooling 117 g of the hydroiodide precipitated and was removed by filtration. The dried filter residue was suspended in methylene chloride (250 ml) and cooled (ice bath), and 35 ml of NaOH (50%) was added slowly. After allowing the mixture to stir at room temperature for 2 hr, the organic phase was separated and the aqueous phase extracted twice with 150 ml of methylene chloride. The combined organic phases were dried (sodium sulfate) and concentrated. On addition of ether and cooling a crystalline precipitate formed. This material was filtered off, washed with ether, and dried in vacuo (30°, 1 mm): 45.7 g (67%); mp 73–75°. Anal. C, H.

By the same procedure 4-methyl-2-methylthio-2-imidazoline (**18c**) was prepared from 4-methylimidazolidine-2-thione in 85% yield. This product failed to crystallize and was used without purification in the reaction with isatoic anhydrides.

4,5-Dimethylimidazolidine-2-thione (18e). A stirred suspen-

sion of 2,3-diaminobutane dihydrochloride (24 g, 0.15 mol) in methylene chloride (200 ml) was treated with NaOH (20 ml, 50% solution) and allowed to stir for 1 hr. The organic phase was separated and the aqueous phase twice extracted with methylene chloride. The combined organic phases were dried over sodium sulfate and added dropwise to a stirred solution of carbon disulfide (12 g, 0.16 mol) in methylene chloride (100 ml). The mixture was allowed to stir for 30 min, after which period the solvent was evaporated to dryness. Water (300 ml) was added and the mixture was stirred and heated under reflux for 18 hr. On partial evaporation of the water (to 100 ml) and cooling (ice bath) a precipitate was formed. This material was filtered off, washed, dried, and recrystallized (methylene chloride–ether) yielding 5.5 g of **18e** (28%), mp 188–194°. Anal. C, H, N.

4,5-Dimethyl-2-methylthio-2-imidazoline (18f). The 4,5-dimethylimidazolidine-2-thione (**18e**) was allowed to react with methyl iodide in the usual manner yielding **18f** as an oil.

Octahydro-2*H*-benzimidazole-2-thione (19a). To a stirred solution of carbon disulfide (63 g, 0.83 mol) in 400 ml of CH_2Cl_2, 1,2-diaminocyclohexane (a mixture of cis and trans isomers) (92.5 g, 0.82 mol) in 100 ml of CH_2Cl_2 was added dropwise keeping the temperature below 20°. The mixture was then allowed to stir at room temperature for 2 hr, after which period the solvent was evaporated. The residue was poured on water (500 ml) contained in a 2-l. beaker and the mixture heated on a steam bath until the foaming ceased. After transfer into a 2-l. flask the reaction mixture was heated under reflux for 18 hr. On cooling a crystalline precipitate was formed which was removed by filtration. The filter cake was washed with water (100 ml) and dried by suction. (The filtrate could be concentrated to obtain a second crop.) The crude material was dissolved in methylene chloride, dried (Na_2SO_4), treated with charcoal, and filtered through Celite. The filtrate was partially evaporated. Addition of diethyl ether caused the reaction product (**19a**) to precipitate, which was collected by filtration: 82.2 g (63%); mp 151–160°. Anal. C, H, N.

Hexahydro-2-methylthio-1*H*-benzimidazole (19). To a stirred suspension of octahydro-2*H*-benzimidazole-2-thione (**19a**, 52 g, 0.33 mol) in ethanol (150 ml), methyl iodide (49 g, 0.35 mol) was added. The solids went into solution and the mixture was allowed to stir overnight. After this time a precipitate had formed which was removed by filtration and washed with ether. The filtrate was concentrated and the newly formed precipitate was filtered off: total weight of crude precipitate 97.7 g. The first fraction (72.7 g) was suspended in 350 ml of methylene chloride and NaOH solution (22 ml, 50%) was added dropwise over a period of 2 hr. The methylene chloride phase was separated, extracted with saturated NaCl solution, dried (sodium sulfate), and concentrated. On addition of ether and cooling (Dry Ice) a precipitate was formed which was collected by filtration and washed with ether: 40.2 g; mp 116–118°. The TLC (10% MeOH–90% chloroform) indicated the presence of two compounds in a ratio of ~8:2, which was used as such for the isatoic anhydride reaction.

A small amount (~2 g) of this product was filtered through a silica gel column (Merck, A.G., no. 60) using chloroform as the solvent. Sufficient material of the major component (eluted first) was obtained to allow full characterization: mp 124–129°. Anal. C, H, N.

10-(*p*-Fluorobenzyl)imidazo[2,1-*b*]quinazolin-5(10*H*)-one (15). A mixture of *p*-fluorobenzyl-2,3-dihydroimidazo[2,1-*b*]quinazolin-5(10*H*)-one (**14**, 10 g, 0.033 mol) and manganese dioxide (26 g, 0.3 mol) in xylene (200 ml) was heated under reflux for 20 hr. The hot solution was filtered through Celite, and the filter cake was washed with chloroform. The filtrate was evaporated to dryness; the residue was dissolved in methylene chloride and treated with charcoal. After filtration the solvent was distilled off and on addition of ether the product began to crystallize. The crude material was removed by filtration and recrystallized from methylene chloride–ether to obtain 3.2 g (32%) of **15**, mp 157–159°. Anal. C, H, N.

2,3-Dihydro-6-(*p*-fluorobenzyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (10). To a cooled and stirred solution of 2,4-dichloroquinazoline (60 g, 0.3 mol) in benzene (600 ml) potassium carbonate (25 g) and ethyleneimine (33 ml, 0.6 mol) were added and after 30 min the mixture was removed from the ice bath and allowed to stir at room temperature for 18 hr. The solvent was evaporated in vacuo and the residue repeatedly extracted with methylene chloride. The combined extracts were washed twice with saturated sodium chloride solution, dried over sodium sulfate, and evaporated. The residue crystallized on addition of methanol. The crude crystalline aziridine **7** (32.0 g, 51%, mp 120–123°) was used directly in the next step.

The crude material from above (**7**, 32 g, 0.16 mol) was dissolved in anhydrous acetone (500 ml) and stirred with 3.2 g (0.021 mol) of NaI for 90 min. The solvent was evaporated in vacuo and the residue treated with methylene chloride. Insoluble material was filtered off and the filtrate extracted with saturated sodium chloride solution, dried (sodium sulfate), and evaporated. The crystalline material which was formed on addition of acetone was filtered off and dried at 50° in vacuo, yielding 28.7 g of **5-chloro-2,3-dihydroimidazo[1,2-*c*]quinazoline (8,** 90%), mp 208–210°. Anal. C, H. This product was dissolved in 500 ml of dioxane, 6 *N* hydrochloric acid (500 ml) was added, and the mixture was heated under reflux for 1 hr. After cooling, the reaction was neutralized with 50% NaOH solution (ice cooling) and the dioxane was removed by evaporation. During this process the **2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (9)** crystallized. It was removed by filtration and recrystallized from methanol to yield 23.2 g of **9** (88%), mp >290° (lit.[8] mp 299–300°).

A solution of **2,3-dihydroimidazo[1,2-*c*]quinazolin-5(6*H*)-one (9)** (15 g, 0.08 mol) in dimethylacetamide (300 ml) was treated with small portions of NaH (4 g, 0.095 mol, 57% in mineral oil, washed three times with pentane) and the mixture was stirred at room temperature for 1 hr. *p*-Fluorobenzyl bromide (15.5 g, 0.082 mol) was added and the stirring was continued for 24 hr. The mixture was concentrated in vacuo (to 100 ml) and poured over ice–water (400 ml). After stirring for 1 hr the precipitate was filtered off and dried. The crude material was recrystallized first from chloroform–ether and then from methylene chloride ether to obtain 18.4 g (72%) of 2,3-dihydro-6-(*p*-fluorobenzyl)imidazo[1,2-*c*]quinazolin-5(6*H*)-one (**10**), mp 148–150°. Anal. C, H, N.

2,3-Dihydro-10-(*p*-fluorobenzyl)imidazo[2,1-*b*]quinazoline-5(10*H*)-thione (16). A mixture of **14** (6 g, 0.02 mol), phosphorus pentasulfide (18 g, 0.08 mol), and pyridine (180 ml) was heated under reflux for 5 hr. The reaction mixture was evaporated to dryness and the residue treated with hot water. The insoluble product was filtered off and washed thoroughly with water. After air-drying, it was dissolved in CH_2Cl_2, treated successively with sodium sulfate, charcoal, and alumina, and filtered through Celite. The filtrate was concentrated and on addition of ether a precipitate was formed. This material was filtered off (5.4 g) and recrystallized from CH_2Cl_2–ether to obtain **16:** 4.8 g (76%); mp 222–224°. After repeated recrystallization no accurate determination for H could be obtained. Anal. Calcd for $C_{19}H_{14}N_3SF$: C, 66.2; H, 4.1. Found: C, 66.1; H, 4.8.

References and Notes

(1) (a) Maumee Chemicals, Commercial Publication: "Chemistry of Isatoic Anhydride"; (b) G. E. Hardtmann, G. Koletar, and O. Pfister *J. Heterocycl. Chem.*, submitted for publication. A representative example for the preparation of isatoic anhydrides is given in procedure A.

(2) E. Ziegler, W. Steiger, and Th. Kappe, *Monatsh. Chem.*, **99,** 1499 (1968).

(3) G. E. Hardtmann, B. S. Huegi, J. H. Gogerty, L. C. Iorio, and H. Barnes, *J. Med. Chem.*, **14,** 878 (1971).

(4) T. Jen, B. Dienel, H. Bowman, J. Petta, A. Helt, and B. Loev, *J. Med. Chem.*, **15,** 727 (1972).

(5) G. G. Van Arman, L. M. Miller, and M. P. O'Malley, *J. Pharmacol. Exp. Ther.*, **133,** 90 (1961).

(6) J. W. Constantine, *J. Pharm. Pharmacol.*, **17,** 384–385 (1965).

(7) S. Irwin, "Pharmacological Techniques in Drug Evaluation", J. H. Nodine and P. E. Siegler, Ed., Yearbook Medical Publishers, Chicago, Ill., 1964, pp 36–54.

(8) R. J. Grout and M. W. Partridge, *J. Chem. Soc.*, 3551 (1960).