Antihypertensive 2-Amino-4(3H)-quinazolinones

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The preparation of a series of amino-4(3H)-quinazolinones is described. Several of these compounds exerted an acute antihypertensive effect in dogs after oral administration, without influencing heart rate. Studies of structure–activity relationships demonstrated dimethylamino, diethylamino, diallylamino, ethylallylamino, and N-methylpiperazino substitution at position 2, and 6,7-dimethoxy substitution in the aromatic ring to be optimal for antihypertensive activity.

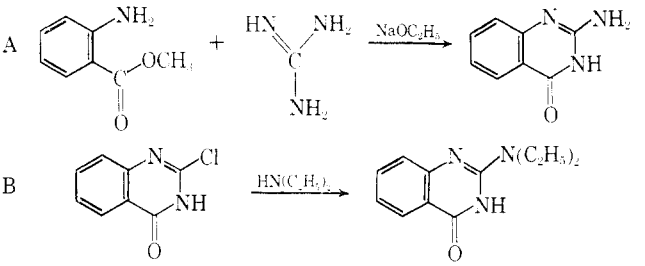
Diverse biological activities have been encountered in compounds having the quinazolinone ring system.[1] For example, the quinazolinone alkaloids, febrifugin[2] and vasicinone,[3] are reputed to elicit antimalarial and bronchodilator activity, respectively. Quinazolinones with CNS activity[4] are known and 2-methyl-3-*o*-tolyl-4(3H)-quinazolinone[5] (methaqualone) has been utilized in therapy as a hypnotic; 2-ethyl-6-sulfonamido-7-chloro-1,2-dihydro-4(3H)-quinazolinone (quinethazone)[6] is a diuretic; other quinazolinones have muscle relaxant,[4e,7] antiinflammatory,[7] antimitotic,[8] antihistaminic,[9] and hypotensive activity.[10]

While numerous 4(3H)-quinazolinones, particularly those with 2-alkyl-3-aryl,[4a–d,11] 2-alkyl-3-alkyl,[12] and 2-alkyl-3-amino[4e,13] substitution, have been prepared and evaluated biologically, 2-amino-4(3H)-quinazolinones have received relatively limited attention.[14] This report summarizes the synthesis and antihypertensive activity of such quinazolinone derivatives.

Synthesis.—2-Amino-4(3H)-quinazolinones with an unsubstituted amino group were prepared in moderate yields from the corresponding methyl anthranilates with excess guanidine in the presence of sodium ethoxide in ethanol (Scheme I, A); the 6-chloro, 7-chloro, 6,7-dimethoxy, and unsubstituted derivatives (Table I, **1**–**4**) were prepared in this fashion. The known nucleophilic displacement of chlorine from 2-chloro-4(3H)-quinazolinone[14b] by amines (Scheme I, B) was utilized

Scheme I

Synthesis of 2-Amino-4(3H)-quinazolinones



as the general synthetic procedure, however, since this route allowed considerably more flexibility in exploring the effects of varying substituents in the heterocyclic ring on activity. Displacements were usually carried out in a closed vessel in ethanolic solution with 2 or more equiv of the appropriate amine at 120–150° for several hours. When high-boiling amines were employed, reaction components were refluxed without solvent. Products in most cases were readily purified by recrystallization or chromatography on Florisil.

The 2-chloro-4(3H)-quinazolinones were obtained by selective alkaline hydrolysis of the corresponding 2,4-dichloroquinazolines at room temperature. Whereas 2,4-dichloroquinazoline can be hydrolyzed in aqueous sodium hydroxide to furnish 2-chloro-4(3H)-quinazolinone,[14b] attempts to hydrolyze 2,4-dichloro-6,7-dimethoxyquinazoline under identical conditions resulted in the recovery of starting material, and treatment of the dichlorodimethoxy derivative with methanolic sodium hydroxide afforded 2-chloro-4,6,7-trimethoxyquinazoline.[15] The desired product could be obtained when the hydrolysis was carried out in aqueous tetrahydrofuran, and all 2,4-dichloroquinazolines were, accordingly, hydrolyzed in this solvent system.

The 2,4-dichloroquinazolines were prepared from 2,4(1H,3H)-quinazolinediones with $POCl_3$ or $POCl_3$–PCl_5 in the presence of N,N-dimethylaniline. The quinazolinediones in turn were obtained by reaction of the anthranilic acids with potassium cyanate, followed

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(14) (a) J. Bunnett, *J. Am. Chem. Soc.*, **68**, 1327 (1946); (b) F. H. S. Curd, J. K. Landquist, and S. L. Rose, *J. Chem. Soc.*, 778 (1947); (c) R. J. Grout and M. W. Partridge, *ibid.*, 3540 (1960); (d) I. Y. Postovskii and I. N. Goncharova, *Zh. Obshch. Khim.*, **32**, 3323 (1962); (e) E. Manolov, *Khim. Ind.* (Sofia), **37**, 372 (1965); *Chem. Abstr.*, **65**, 711 (1966); (f) K. Hartke, R. Alarcon, D. Ramirez, and J. Bartulin, *Arch. Pharm.*, **299**, 914 (1966).

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by treatment with aqueous sodium hydroxide, without isolation of the intermediate urea derivatives.[16]

The starting material for the required 4,5-dialkoxyanthranilic acids was methyl 3,4-dihydroxybenzoate. Alkylation of this substance with the appropriate alkyl bromides, followed by nitration,[17] stannous chloride reduction, and, finally, alkaline hydrolysis, gave the desired products.

To prepare 4,5-dimethylanthranilic acid,[18] the Diels–Alder adduct of 2,3-dimethylbutadiene and maleic anhydride[19] was treated with ammonia, and the resulting 4,5-dimethyl-Δ^4-tetrahydrophthalimide[20] was dehydrogenated with iodine and sulfur in refluxing decalin to afford 4,5-dimethylphthalimide.[21] This substance was hydrolyzed with sodium hydroxide to 4,5-dimethylphthalamic acid which, without purification, was subjected to a Hofmann reaction to furnish the desired product.

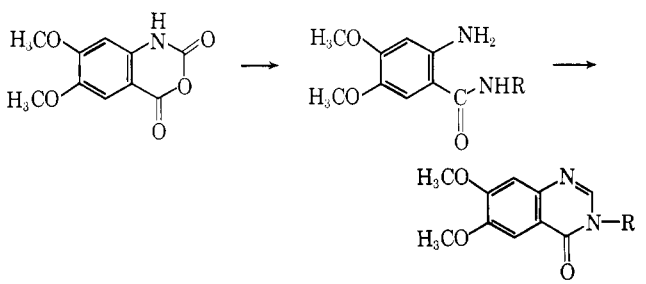
Treatment of the O-methyl-substituted 2-amino-4(3H)-quinazolinones with refluxing, aqueous 48% hydrobromic acid resulted in O-demethylation and furnished the phenolic compounds (**46–48**).

3-Methyl- and 3-*o*-tolyl-substituted 2-amino-6,7-dimethoxy-4(3H)-quinazolinones were prepared in the following manner. Reaction of methyl 3,4-dimethoxyanthranilate with methyl or *o*-tolyl isocyanate in pyridine, followed by treatment with methanolic sodium hydroxide, afforded 3-methyl- and 3-*o*-tolyl-6,7-dimethoxy-2,4(1H,3H)-quinazolinedione, respectively. These substances were converted with $POCl_3$ to 2-chloro derivatives,[22] which were treated without purification with diethylamine at 140° to afford **52** and **53**.

Representative 3-amino-6,7-dimethoxy-4(3H)-quinazolinones, which are isomeric with the 2-amino-4(3H)-quinazolinones, were synthesized from 4,5-dimethoxyisatoic acid anhydride (Scheme II) which, in turn, was

SCHEME II

SYNTHESIS OF 3-AMINO-4(3H)-QUINAZOLINONES



synthesized from 4,5-dimethoxyanthranilic acid and phosgene. The anhydride was treated with the appropriate hydrazines in chloroform or dimethylformamide to form the corresponding hydrazides, and these, in refluxing formic acid, were converted to the desired 3-amino-4(3H)-quinazolinones[4e] (**54–57**, R = dimethylamino, diethylamino, N-morpholino, and N-homopiperidino).

Pharmacological Methods.—The amino-4(3H)-quinazolinones were evaluated for antihypertensive activity in dogs made hypertensive by the procedure of Goldblatt, *et al.*;[23] the systolic arterial blood pressure of these dogs ranged from 160–200 mm. Doses of 2.5, 10.0, and 40.0 mg/kg were administered orally in capsules on consecutive days, generally in the form of hydrochlorides (see Table I). In a few instances only one or two doses were administered. The systolic pressure was determined on the coccygeal artery according to the method of Prioli and Winbury[24] prior to drug administration and 2, 4, and 24 hr thereafter. Heart rates were determined from the simultaneously recorded ECG. The maximum antihypertensive response was generally observed at the 2-hr measurement. Two dogs were used for evaluation of each compound. An average blood pressure decrease of less than 10 mm was assigned a score of 0; decreases of 10–20, 20–35, and 35–60 mm were scored +, ++, and +++, respectively.

Structure–Activity Study.—The initial discovery that 2-amino-6,7-dimethoxy-4(3H)-quinazolinone (**1**), but not the corresponding 6-chloro, 7-chloro, and unsubstituted derivatives, had antihypertensive activity prompted a thorough investigation of related, 6,7-dimethoxy-substituted 2-amino-4(3H)-quinazolinones. It was found in these studies that substitution of the amino group greatly improved activity. For example, whereas **1** produced an antihypertensive response of 30 mm at 40 mg/kg and no significant response at lower doses, the dimethylamino analog **5** decreased the blood pressure by 40 mm at 10 mg/kg (see Table I). The 2-diethylamino-6,7-dimethoxy-4(3H)-quinazolinone (**6**) was even more potent and lowered the blood pressure by 20 mm at 2.5 mg/kg and by 60 mm at 10 mg/kg; the duration of action was longer than 4 but shorter than 24 hr and appeared to vary with the dose. Lengthening of the alkyl chain, as exemplified by the di-*n*-propylamino (**10**) and di-*n*-butylamino (**11**) analogs, markedly diminished activity, but the ethylallylamino (**7**) and diallylamino (**8**) derivatives were active at 10 mg/kg (decreases of 30 and 40 mm, respectively). One of the more potent compounds with a heterocyclic substituent was the N-methylpiperazino derivative **16**, which elicited a 35-mm response at 10 mg/kg. The pyrrolidino (**12**), piperidino (**13**), hexamethylenimino (**14**), and heptamethylenimino (**15**) analogs exerted good activity at the 40-mg/kg dose. Monoalkylamino derivatives, including benzylamino and phenethylamino, were only weakly active or inactive with the exception of the isopropylamino (**22**) derivative which lowered the blood pressure by 30 mm at 40 mg/kg and had a somewhat smaller effect at 10 mg/kg.[25] It is

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(17) Nitration of the methyl esters furnished consistently better yields than direct nitration of the benzoic acids.

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(22) H. T. Bogert and C. E. May, *J. Am. Chem. Soc.*, **31**, 507 (1909), reported the loss of a 3-methyl substituent during the chlorination of 2,3-dimethyl-4(3H)-quinazolinone with PCl_5–$POCl_3$. The fact that 2-diethylamino-3-methyl-6,7-dimethoxy-4(3H)-quinazolinone was the only substance isolated in the preparation of the 3-methyl derivative is consistent with the milder chlorinating properties of $POCl_3$ alone. See also, R. F. Smith and R. A. Kent, *J. Org. Chem.*, **30**, 1312 (1965).

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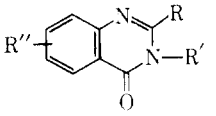
(25) Solubility differences between the hydrochlorides of the lower dialkylamino (**5**, **6**) and the isopropylamino (**22**) derivatives on the one hand and the monoalkylamino derivatives **18–20**, as well as compounds **10** and **11**, on the other hand were noted. Whereas **5**, **6**, and **22** were readily soluble, **10**, **11**, and **18–20** had low solubility in aqueous solution. Low solubility could hamper oral absorption, and this may account, in part, for the observed differences in activity.

Table I

Amino-4(3H)-quinazolinones



No.	R	R′	R″	Mp, °C	Yield, %	Crystn solvent[a]	Formula[c]	Hydrochloride mp, °C	Activity at mg/kg 2.5	10.0	40.0
1	NH_2	H	6,7-OCH_3	317–319	43	D	$C_{10}H_{11}N_3O_3$	267–269		0	++
2	NH_2	H	6-Cl	370–375	32	D–W	$C_8H_6ClN_3O$				0
3	NH_2	H	7-Cl	397–400	54	D	$C_8H_6ClN_3O \cdot HCl$	>400			0
4	NH_2[b]	H	H	>400	66	D	$C_8H_7N_3O$				0
5	$N(CH_3)_2$	H	6,7-OCH_3	246–248	87	D–W	$C_{12}H_{15}N_3O_3$	279–282	0	++	+++
6	$N(C_2H_5)_2$	H	6,7-OCH_3	216–217	75	M	$C_{14}H_{19}N_3O_3$	250–251	+	+++	+++
7	$N(C_2H_5)CH_2CH{=}CH_2$	H	6,7-OCH_3	183–185	50	E	$C_{15}H_{19}N_3O_3$	239–240	0	++	
8	$N(CH_2CH{=}CH_2)_2$	H	6,7-OCH_3	190–191	75	I	$C_{16}H_{19}N_3O_3$	233–235	0	++	+++
9	$N(CH_2CH_2OH)_2$	H	6,7-OCH_3	189–193	52	M–E	$C_{14}H_{19}N_3O_5$[f]		0	+	+
10	$N(CH_2CH_2CH_3)_2$	H	6,7-OCH_3	197–200	58	M	$C_{16}H_{23}N_3O_3$	237–239			0
11	$N(CH_2CH_2CH_2CH_3)_2$	H	6,7-OCH_3	165–167	85	M	$C_{18}H_{27}N_3O_3$				0
12		H	6,7-OCH_3	246–249	97	A	$C_{14}H_{17}N_3O_3$	269–271		0	++
13		H	6,7-OCH_3	263–265	85	C	$C_{15}H_{19}N_3O_3$	256–257		0	++
14		H	6,7-OCH_3	253–255	83	A	$C_{16}H_{21}N_3O_3$	244–245		0	++
15		H	6,7-OCH_3	237–238	90	A	$C_{17}H_{23}N_3O_3$	222–224	0	+	+++
16		H	6,7-OCH_3	250–252	78	M–E	$C_{15}H_{20}N_4O_3$	242–246[e]	0	++	+++
17		H	6,7-OCH_3	316–318	84	M	$C_{16}H_{21}N_3O_4$	277–281		0	+
18	$NHCH_3$	H	6,7-OCH_3	294–296	72	D	$C_{11}H_{13}N_3O_3 \cdot 0.5H_2O$	334–336			0
19	NHC_2H_5	H	6,7-OCH_3	262–264	77	A	$C_{12}H_{15}N_3O_3$	293–294			0
20	$NHCH_2CH_2CH_3$	H	6,7-OCH_3	216–218	92	A	$C_{13}H_{17}N_3O_3 \cdot HCl$	299–300		0	+
21	$NHCH_2CH_2OC_2H_5$	H	6,7-OCH_3	180–183	60	A	$C_{14}H_{19}N_3O_4$[g]				0
22	$NHCH(CH_3)_2$	H	6,7-OCH_3	244–246	43	M	$C_{13}H_{17}N_3O_3 \cdot HCl$	283–285	0	+	++
23	$NHCH_2CH_2OH$	H	6,7-OCH_3	239–240	92	A	$C_{12}H_{15}N_3O_4$			+	+
24	$NHNH_2$	H	6,7-OCH_3	284–285	91	G	$C_{10}H_{12}N_4O_3$	264–266			0
25	$NHCH_2C_6H_5$	H	6,7-OCH_3	245–247	82	I	$C_{17}H_{17}N_3O_3$				0
26	$NHCH_2CH_2C_6H_5$	H	6,7-OCH_3	229–231	77	A	$C_{18}H_{19}N_3O_3$				0
27	NHC_6H_5	H	6,7-OCH_3	267–270	78	A	$C_{16}H_{15}N_3O_3$				0
28	$N(CH_3)CH_2C_6H_5$	H	6,7-OCH_3	216–221	92	D–W	$C_{18}H_{19}N_3O_3$	255–258			+
29	$N(C_2H_5)_2$	H	6,7-OC_2H_5	196–199	77	C–A	$C_{16}H_{23}N_3O_3$[b]	193–197	0	+	++
30	$N(CH_3)_2$	H	6,7-$OCH(CH_3)_2$	195–196	61	E	$C_{16}H_{23}N_3O_3$	229–231			0
31	$N(C_2H_5)_2$	H	6,7-$OCH(CH_3)_2$	141–143	60	M–W	$C_{18}H_{17}N_3O_3$	126–132		0	
32	$N(CH_3)_2$	H	6,7-OCH_2O	298–299	83	D	$C_{11}H_{11}N_3O_3$	303–306			0
33	$N(C_2H_5)_2$	H	6,7-OCH_2O	271–274	83	M	$C_{13}H_{15}N_3O_3$	261–264			0
34	$N(CH_3)_2$	H	6,7-O-$(CH_2)_2O$	291–292	47	M	$C_{12}H_{13}N_3O_3$	325–328			0
35	$N(C_2H_5)_2$	H	6,7-O-$(CH_2)_2O$	240–241	82	A	$C_{14}H_{17}N_3O_3$	239–241			0
36	$N(CH_3)_2$	H	6-OCH_3	216–219	51	A	$C_{11}H_{13}N_3O_2$	260–264			0
37	$N(C_2H_5)_2$	H	6-OCH_3	193–196	63	A	$C_{13}H_{17}N_3O_2$	209–212		0	++
38	$N(CH_3)_2$	H	7-OCH_3	257–261	74	A	$C_{11}H_{13}N_3O_2$	266–268	0	+	++
39	$N(C_2H_5)_2$	H	7-OCH_3	190–193	65	A	$C_{13}H_{17}N_3O_2$	215–218	0	++	
40	$N(CH_3)_2$	H	8-OCH_3	254–257	62	D–W	$C_{11}H_{13}N_3O_2$	223–226		0	
41		H	8-OCH_3	255–259	62	A	$C_{14}H_{18}N_4O_2$	305–310[e]			0
42	$N(CH_2CH{=}CH_2)_2$	H	6-Cl	217–220	77	D	$C_{14}H_{14}ClN_3O$	204–208			0
43	$N(C_2H_5)_2$	H	6-Cl	283–286	85	D	$C_{12}H_{14}ClN_3O$	274–281			0
44	$N(CH_3)_2$	H	H	239–241	84	A	$C_{10}H_{11}N_3O$	279–282			0
45	$N(C_2H_5)_2$	H	H	177–180	88	A	$C_{12}H_{15}N_3O$	244–248			0
46	$N(C_2H_5)_2$	H	7-OH	309–311[d]	90	A–H	$C_{12}H_{15}N_3O_2 \cdot HBr$				0

TABLE I (*Continued*)

No.	R	R′	R″	Mp, °C	Yield, %	Crystn solvent[a]	Formula[e]	Hydrochloride mp, °C	Activity at mg/kg 2.5	10.0	40.0
47	$N(C_2H_5)_2$	H	6,7-OH	296–300	62	M	$C_{12}H_{15}N_3O_3$	304–306			0
48	$N(C_2H_5)_2$	H	8-OH	280–283[d]	67	A–H	$C_{12}H_{15}N_3O_2 \cdot HBr$[i]				0
49	$N(C_2H_5)_2$	H	7-Cl	220–223	61	A	$C_{12}H_{14}ClN_3O$	237–241			0
50	$N(CH_3)_2$	H	6,7-CH_3	286–288	31	D	$C_{12}H_{15}N_3O \cdot HCl$	301–303	0	++	
51	$N(C_2H_5)_2$	H	6,7-CH_3	253–254	61	A	$C_{14}H_{19}N_3O$	237–239		+	++
52	$N(C_2H_5)_2$	CH_3	6,7-OCH_3	131–133	43	E–P	$C_{15}H_{21}N_3O_3$	218–220			0
53	$N(C_2H_5)_2$	o-$CH_3C_6H_4$	6,7-OCH_3	155–158	30	C–P	$C_{21}H_{21}N_3O_3$				0
54	H	$N(CH_3)_2$	6,7-OCH_3	174–176	52	M	$C_{12}H_{15}N_3O_3$				0
55	H	$N(C_2H_5)_2$	6,7-OCH_3	112–114	55	P	$C_{14}H_{19}N_3O_3 \cdot HCl$	230–232		0	
56	H		6,7-OCH_3	239–240	32	A	$C_{14}H_{17}N_3O_4$				0
57	H		6,7-OCH_3	165–166	34	A	$C_{16}H_{21}N_3O_3$			0	

[a] A, EtOH; C, $CHCl_3$; D, DMF; E, EtOAc; G, ethylene glycol; H, 48% HBr; I, *i*-PrOH; M, MeOH; P, isopropyl ether; W, H_2O. [b] K. Kunckel, *Chem. Ber.*, **38**, 1214 (1905). [c] Dihydrochloride. [d] Hydrobromide. [e] All compounds were analyzed for C, H, N. [f] *Anal.* N: calcd, 13.59; found, 12.99. [g] *Anal.* C: calcd, 57.43; found, 57.00. [h] *Anal.* H: calcd, 7.59; found, 7.12. [i] *Anal.* C: calcd, 45.87; found, 45.45.

noteworthy that the antihypertensive responses were not accompanied by any changes in heart rate.

To investigate substitution requirements in the aromatic ring in more detail, 6,7-diethoxy, 6,7-diisopropoxy, 6,7-methylenedioxy, 6,7-ethylenedioxy, 6,7-dimethyl, 6,7-dihydroxy, 6-methoxy, 6-chloro, 7-methoxy, 7-hydroxy, 8-methoxy, and 8-hydroxy as well as unsubstituted derivatives were examined. Dimethylamino, diethylamino, diallylamino, or N-methylpiperazino were chosen as substituents at the 2 position, since these had produced best activity in the 6,7-dimethoxy-substituted series. However, only the 6,7-dimethyl (**50**, **51**) and the 6,7-diethoxy (**29**) and 7-methoxy derivatives (**38**, **39**) approached the potency exhibited by the corresponding 6,7-dimethoxy analogs. Other alkoxy substituents reduced activity and the chloro (**42**, **43**, **49**), phenolic (**46**–**48**), and unsubstituted **44**, **45**) derivatives were inactive.

The fact that the 3-methyl (**52**) and 3-*o*-tolyl (**53**) derivatives were inactive may indicate that a dissociable hydrogen atom in position 3 is a requirement for antihypertensive activity. Conceivably, the 4-hydroxyquinazoline rather than the 4(3H)-quinazolinone form is the biologically active species. In agreement with this is the observation that the 3-amino-substituted 4(3H)-quinazolinones (**54**–**57**), which are isomeric with the antihypertensive 2-amino-4(3H)-quinazolinones, were devoid of antihypertensive activity.

Recently, Pala and Marazzi-Uberti[26] reported that 2,4(1H,3H)-quinazolinedione as well as some related derivatives produced hypotensive responses in cats. Several of our structurally similar synthetic intermediates, such as 6,7-dimethoxy-2,4(1H,3H)-quinazolinedione and 2-chloro-6,7-dimethoxy-4(3H)-quinazolinone, were therefore evaluated for antihypertensive activity. However, in our hands neither these nor 2,4-(1H,3H)-quinazolinedione had activity when examined in dogs at 40 mg/kg.

In summary, good antihypertensive activity is observed in this series of 4(3H)-quinazolinones when the 2 substituent is dimethylamino, diethylamino, diallylamino, ethylallylamino, or 4-methylpiperazino, the 3 position is unsubstituted, and the aromatic ring is 7-methoxy, 6,7-diethoxy, 6,7-dimethyl, or 6,7-dimethoxy substituted. Maximal activity is seen in the 2-diethylamino-6,7-dimethoxy derivative (**6**).

Pharmacological studies on the mechanism of action of 2-diethylamino-6,7-dimethoxy-4(3H)-quinazolinone (**6**) indicate that the antihypertensive activity of this substance is the result of reduced, peripheral, vascular resistance; a component of direct relaxation of vascular smooth muscle appears to be a contributory factor to this action. The compound does not elicit ganglionic blocking properties in cats, nor does it lower the cardiac output of anesthetized dogs. There was no indication of the development of tolerance after oral administration of 5 mg/kg of **6** for 10 consecutive days to conscious hypertensive dogs. Preliminary clinical results suggest that **6** lowers the blood pressure of hypertensive human subjects.[27] A report on the metabolism of **6** in humans has recently been published.[28]

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

Melting points (Thomas–Hoover capillary melting point apparatus) are uncorrected. Uv spectra were measured on a Cary recording spectrometer in EtOH solution, nmr spectra in $CDCl_3$ solution (TMS) on a Varian A-60 spectrometer. 2-Chloro-4(3H)-quinazolinone[14b] and the 6-chloro-, 6-methoxy-, 7-chloro-, 7-methoxy-, 6,7-dimethoxy-, and 8-methoxy-substituted 2,4-dichloroquinazolines[16] were prepared by published procedures.

Methyl 3,4-Diethoxy-6-nitrobenzoate.—To 205 g (0.91 mole) of methyl 3,4-diethoxybenzoate[29] in 450 ml of glacial AcOH was added over a period of 1.5 hr, 895 ml of HNO_3 (sp gr 1.42) at such a rate that the temperature did not exceed 45°. The mixture was stirred at room temperature for 1 hr, then poured with vigorous stirring slowly into 3.5 l. of ice–H_2O, and dried to give 214.5 g (85%) of the desired product. The analytical sample was recrystallized from C_6H_6–hexane; mp 74–77°. *Anal.* ($C_{12}H_{15}NO_6$) C, N; H: calcd, 5.26; found, 5.68.

Methyl 3,4-Diethoxy-6-aminobenzoate.—A solution of 652 g of anhydrous $SnCl_2$ in 2.8 l. of concentrated HCl was stirred

(26) G. Pala and E. Marazzi-Uberti, *Arzneimittel-Forsch.*, **12**, 1204 (1962).

(27) T. F. Brewer, 1967, personal communication.

(28) M. Schach von Wittenau, and T. F. Brewer, *J. Med. Chem.*, **10**, 729 (1967).

(29) M. Tomita and T. Kugo, *J. Pharm. Soc. Japan*, **75**, 1350 (1955).

at 26° under N_2, as 209.5 g of methyl 3,4-diethoxy-6-aminobenzoate was added over a period of 1 hr (temperature during addition, 26–30°). The slurry was stirred at 25° for 2 hr, diluted with 815 ml of concentrated HCl, and filtered. The collected solids were washed with HCl and dissolved in 9 l. of H_2O; the filtrate was made alkaline with NH_4OH. The precipitate was washed with H_2O and dried to give 173 g (93%) of product, mp 85–90°. The analytical sample had mp 95–98°. *Anal.* ($C_{12}H_{17}NO_4$) C, H, N.

3,4-Diethoxy-6-aminobenzoic Acid.—To 173 g (0.73 mole) of methyl 3,4-diethoxy-6-aminobenzoate was added 2.18 l. of 1 *N* NaOH solution (MeOH–H_2O, 4:1), and the mixture was refluxed for 2 hr. The solvent was evaporated, the residue was dissolved in 5 l. of H_2O, and the solution was acidified with AcOH to pH 4. The slurry was stirred for 30 min at 5° to give 146 g (90%) of product. The analytical sample (EtOH–H_2O) had mp 156–158° (lit.[30] mp 135–136°). *Anal.* ($C_{11}H_{15}N_4O$) C, H, N.

Methyl 3,4-Diisopropoxybenzoate.—A suspension containing 168.0 g (1.0 mole) of methyl 3,4-dihydroxybenzoate, 276 g (2.0 moles) of K_2CO_3, and 420 g (3.4 moles) of 2-bromopropane in 1.35 l. of MeOH was stirred at reflux for 68 hr. The resulting mixture was evaporated to dryness and dissolved in 1 l. of H_2O. The solution was extracted with three 500-ml portions of CH_2Cl_2, and the combined extracts were washed with 1 *N* NaOH solution and H_2O. The organic layer afforded 240 g (96%) of a pale yellow oil. *Anal.* ($C_{14}H_{20}O_4$) C, H.

Methyl 3,4-Diisopropoxy-2-nitrobenzoate.—To a stirred solution of 200 g (0.79 mole) of methyl 3,4-diisopropoxybenzoate in 350 ml of AcOH was added over 1 hr, a solution of 700 ml of HNO_3 (sp gr 1.42) in 350 ml of AcOH. The reaction was exothermic, and the temperature was maintained at 28°. The solution was stirred at room temperature for 1.5 hr, then poured into *ca.* 8 kg of ice with vigorous stirring. The resulting solids were collected and washed with H_2O to give 220.6 g (94%) of a yellow solid, mp 56–58°. The analytical sample (MeOH–H_2O) had mp 62–63°. *Anal.* ($C_{14}H_{19}NO_6$) C, H, N.

Methyl 6-Amino-3,4-diisopropoxybenzoate.—To 535 g (2.37 moles) of $SnCl_2 \cdot 2H_2O$ in 1.9 l. of concentrated HCl was added in portions, 200 g (0.68 mole) of methyl 3,4-diisopropoxy-6-nitrobenzoate, keeping the temperature below 30°. The suspension was stirred at room temperature for 2 hr, diluted with 800 ml of concentrated HCl and cooled to 10°. The filtered material was slurried in 8.0 l. of H_2O, cooled to 8°, and made basic with concentrated NH_4OH; the mixture was filtered. The solid was suspended in 4 l. of hot CH_2Cl_2 and filtered and the filtrate was concentrated to give 120 g (67%) of a brown crystalline solid, mp 82–84°. Extraction of the insoluble material with boiling MeOH provided an additional 60.0 g (33%) of product, mp 82–84°. The analytical sample (MeOH–H_2O) had mp 99–101°. *Anal.* ($C_{14}H_{21}NO_4$) C, H, N.

6-Amino-3,4-diisopropoxybenzoic Acid.—A mixture of 179 g (0.68 mole) of methyl 6-amino-3,4-diisopropoxybenzoate and 2 l. of 1 *N* NaOH (4:1, MeOH–H_2O) was stirred at reflux for 3 hr. The MeOH was evaporated and 1 l. of H_2O was added. The solution was adjusted to pH 6.0 with AcOH, and the solid was filtered to afford 133 g (78%) of beige, crystalline product, mp 160–161°. The analytical sample (MeOH) had mp 169–170°. *Anal.* ($C_{13}H_{19}NO_4$) C, H, N.

6-Carbomethoxy-1,4-benzodioxane.—A mixture of 250 g (1.5 moles) of methyl 3,4-dihydroxybenzoate, 415 g (3.0 moles) of K_2CO_3, and 935 g (5.1 moles) of 1,2-dibromoethane in 2 l. of MeOH was stirred at reflux for 18 hr. The suspension was evaporated, and 1 l. of H_2O was added. The mixture was extracted with CH_2Cl_2. After removal of the solvent the residual oil crystallized under high vacuum to furnish 284 g (98%) of a white, crystalline solid, mp 40°. Lipp, *et al.*,[31] described 6-carbomethoxy-1,4-benzodioxane as an oil.

6-Carbomethoxy-7-amino-1,4-benzodioxane.—To 12.0 g (0.05 mole) of $SnCl_2 \cdot 2H_2O$ in 40 ml of concentrated HCl was added 3.6 g (0.015 mole) of 6-carbomethoxy-7-nitro-1,4-benzodioxane;[30] the mixture was stirred for 3 hr. The suspension was filtered, the solid material was washed with cold concentrated HCl, dissolved in 70 ml of H_2O, and filtered, and the filtrate was made basic with concentrated NH_4OH. The precipitate furnished 3.15 g (100%) of a beige solid, mp 82–85° (lit.[31] mp 81°). Saponification of this material with 1 *N* NaOH (4:1, MeOH–H_2O) gave 7-amino-1,4-benzodioxane-6-carboxylic acid as beige needles, mp 195–196° (MeOH) (lit.[32] mp 191–192°).

6-Aminopiperonylic Acid.—A suspension of 135.5 g (0.70 mole of methyl 6-aminopiperonylate[33] in 2.1 l. of 1 *N* NaOH (4:1, MeOH–H_2O) was heated at reflux for 2 hr. The MeOH was evaporated and 500 ml of H_2O was added. The solution was cooled to 0° and acidified to pH 4.5 with AcOH. The resulting solid (121.4 g, 97%) had mp 186–188°. *Anal.* ($C_8H_7NO_4$) C, H, N.

4,5-Dimethyl-Δ^4-tetrahydrophthalimide.—Reaction of 2,3-dimethylbutadiene with maleic anhydride in C_6H_6 produced the Diels–Alder adduct in 85% yield, mp 75–78° (lit.[19] mp 78°). This, on treatment with NH_3[32] at 200°, produced (75% yield) the tetrahydrophthalimide, mp 121–124° (lit.[20] mp 126.5–127).

4,5-Dimethylphthalimide.—A mixture of 67.0 g (0.38 mole) of 4,5-dimethyl-Δ^4-tetrahydrophthalimide, 29.6 g (0.925 g-atom) of S, 13.5 g of Ph_2O, 0.4 g of I_2, and 400 ml of decalin was heated for 6 hr at 190°.[34] A complete solution was attained at 130° and copious evolution of H_2S occurred at 190°. After cooling, the mixture was filtered, and the solid was washed with anhydrous Et_2O to afford 56.6 g (85%) of product, mp 228–232°. Recrystallization of a sample from MeOH–CH_2Cl_2 gave material of mp 236–238° (lit.[21a] mp 241–242°).

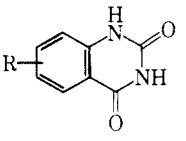
4,5-Dimethylanthranilic Acid.—A suspension of 55.0 g (0.309 mole) of 4,5-dimethylphthalimide in 328 ml of 1 *N* NaOH was heated to 90° on a steam cone (temperature attained in 6.5 min). The solution was filtered while hot, and the cooled filtrate was acidified with concentrated HCl to pH 1.0. The resulting precipitate was filtered and dried to yield 52.5 g (88%) of 4,5-dimethylphthalamic acid as an amorphous solid, mp 140–144° dec (resolidifies at 228–232°). This material (0.272 mole) was added to a NaOCl solution prepared from Cl_2 gas (21.7 g, 0.306 mole) which was bubbled into 163.8 g (4.07 moles) of NaOH and 216 g of ice. The temperature rose to 45° during the addition, and after 15 min the mixture was heated at 55° for 40 min. The resulting solution was cooled in an ice–H_2O bath and acidified to pH 4.0 with AcOH. The precipitate was filtered, to yield 34.0 g (76%) of product, mp 193–195° dec (lit.[18] mp 213–214° dec).

6,7-Diethoxy-2,4(1H,3H)-quinazolinedione.—To a stirred mixture of 73 g of 3,4-diethoxy-6-aminobenzoic acid, 2.2 l. of H_2O, and 36 ml of AcOH was added a solution of KOCN (57.8 g) in 200 ml of H_2O over a period of 1 hr. The temperature during the addition was maintained at 30°. After stirring the mixture for 1.5 hr, NaOH pellets (650 g) were added portionwise. The mixture was stirred at 90° for 30 min, cooled to room temperature, and acidified with concentrated HCl. The solids were filtered to furnish 66 g (73%) of the desired product, mp 256–259°. *Anal.* ($C_{12}H_{14}N_2O_4$) C, H, N.

The corresponding 6,7-methylenedioxy, 6,7-ethylenedioxy, 6,7-diisopropoxy, and 6,7-dimethyl derivatives were prepared similarly. Yields and melting points of these compounds are summarized in Table II.

TABLE II

2,4(1H,3H)-QUINAZOLINEDIONES



R	Yield, %	Mp, °C
6,7-OCH_2O	90	>400
6,7-OCH_2CH_2O	94	364–366
6,7-$OCH(CH_3)_2$	79	248–250
6,7-CH_3	90	350–354

6,7-Diethoxy-2,4-dichloroquinazoline.—To 64 g of 6,7-diethoxy-2,4(1H,3H)-quinazolinone in 160 ml of $POCl_3$ was added over a period of 30 min, 16 ml of N,N-dimethylaniline. The mixture was then heated at reflux for 3 hr (complete solution occurred after 15 min). The $POCl_3$ was removed *in vacuo*, the remaining oil was poured into 3 l. of ice–H_2O, and the resulting

(30) J. Szabo and E. Vinkler, *Acta Chim. Acad. Sci. Hung.*, **17**, 201 (1958).

(31) M. Lipp, F. Dallacker, and R. Schaffranick, *Chem. Ber.*, **91**, 2247 (1958).

(32) P. M. Heertjes, B. J. Knape, H. C. A. van Beek, and K. van den Boogart, *J. Chem. Soc.*, 3445 (1957).

(33) (a) F. Dallacker, *Monatsh.*, **90**, 846 (1959); (b) E. Oertly and A. Pictet, *Chem. Ber.*, **43**, 1336 (1910).

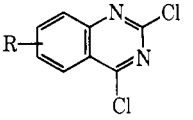
(34) E. Schefczik, *ibid.*, **98**, 1280 (1965).

mixture was extracted with $CHCl_3$. Evaporation of the solvent provided a crystalline residue which was recrystallized from CH_2Cl_2–MeOH to give 62 g of the product.

The corresponding 6,7-methylenedioxy, 6,7-ethylenedioxy, 6,7-diisopropoxy, and 6,7-dimethyl derivatives were prepared similarly. Yields, melting points, and analytical data are summarized in Table III.

TABLE III

2,4-DICHLOROQUINAZOLINES



R	Yield, %	Mp, °C	Formula[a]
6,7-OC_2H_5	97	172–174	$C_{12}H_{12}Cl_2H_2O_2$
6,7-OCH_2O	83	217–218	$C_9H_4Cl_2N_2O_2$
6,7-OCH_2CH_2O	67	221–223	$C_{10}H_6Cl_2N_2O_2$
6,7-$OCH(CH_3)_2$	83	100–102	$C_{14}H_{16}Cl_2N_2O_2$
6,7-CH_3	78	138–410	$C_{10}H_8Cl_2N_2$

[a] All compounds were analyzed for C, H, Cl, N.

2-Chloro-4,6,7-trimethoxyquinazoline.—To 2.95 g (0.01 mole) of 2,4-dichloro-6,7-dimethoxyquinazoline was added 22 ml of 1 *N* NaOH (4:1, MeOH–H_2O), and the mixture was stirred at room temperature for 5 hr. Removal of the solvent afforded a residue which was triturated in H_2O. The insoluble crystalline material (2.2 g, mp 196–200°) was recrystallized from 150 ml of EtOH to furnish 1.6 g (64%) of product: mp 201–204°; λ_{max} 239, 310, 323 mμ (ε 48,800, 6820, 7600); nmr absorption at τ 5.8 (singlet, 3 protons of 4-OCH_3) and 5.99 (singlet, 6 protons of 6,7-OCH_3). *Anal.* ($C_{11}H_{11}ClN_2O_3$) C, H, Cl, N.

2-Chloro-6,7-dimethoxy-4(3H)-quinazolinone.—A mixture of 950 ml of 1 *N* NaOH, 300 ml of THF, and 41 g of 2,4-dichloro-6,7-dimethoxyquinazoline was stirred at room temperature under N_2 for 4 hr. The solution was chilled and adjusted to pH 5 with AcOH; the light yellow solids which precipitated were filtered to give 37.7 g (99%) of product, mp 270–272°. *Anal.* ($C_{10}H_9ClN_2O_3$) C, H, N.

The 6-chloro, 7-chloro, 6-methoxy, 7-methoxy, 8-methoxy, 6,7-methylenedioxy, 6,7-ethylenedioxy, 6,7-diethoxy, 6,7-diisopropoxy, and 6,7-dimethyl derivatives were prepared similarly. The melting points of these substances and the yields realized are summarized in Table IV.

2-Amino-6,7-dimethoxy-4(3H)-quinazolinone (1).—To 21.2 g of methyl 3,4-dimethoxyanthranilate in 100 ml of EtOH was added an ethanolic solution (350 ml) of guanidine (0.5 mole), prepared from guanidine hydrochloride (0.5 mole) and 0.6 g-atom of Na in EtOH. The suspension was refluxed for 100 hr and concentrated to dryness. The residue, in 150 ml of H_2O was acidified with AcOH to pH 5, and the crystalline precipitate was collected; mp 263–274°. Recrystallization from 500 ml of DMF furnished 10.7 g of product, λ_{max} 239, 326 mμ (ε 41,660, 5470), shoulders at 243, 265, 275 mμ.

2-Diethylamino-6,7-dimethoxy-4(3H)-quinazolinone (6).—To 2-chloro-6,7-dimethoxy-4(3H)-quinazolinone (6.7 g) in 60 ml of EtOH was added 32 ml of Et_2NH, and the mixture was heated to 130° in a pressure bottle for 5 hr. The clear solution was cooled to 0°, and the precipitate was filtered to afford 7.16 g of the desired product: λ_{max} 242, 277, 287, 319, 330 mμ (ε 39,640, 9017, 9278, 6011, 6142); nmr absorption at τ −1.2 (singlet, proton in position 3, exchanged with D_2O), 2.57 (singlet, proton assigned to position 5), 3.2 (singlet, proton in position 8), 6.03, 6.07 (doublet, 6 protons of 6,7-OCH_3), 6.32 (quartet, 4 CH_2 protons of $-N(CH_2CH_3)_2$), 8.74 (triplet, 6 CH_3 protons of $-N(CH_2CH_3)_2$).

The **hydrochloride** was prepared in EtOH with anhydrous HCl. *Anal.* ($C_{14}H_{19}N_3O_3 \cdot HCl$) C, H, N.

2-(N-Bis-β-hydroxyethyl)-6,7-dimethoxy-4(3H)-quinazolinone (9).—To 4.8 g of 2-chloro-6,7-dimethoxy-4(3H)-quinazolinone was added 30 ml of diethanolamine, and the mixture was heated to 130°. After 2 hr, the solution was cooled to 0°, 50 ml of cold EtOH was added, and the precipitate was filtered to afford 3.2 g of **9** which was recrystallized from MeOH–EtOAc.

2-Isopropylamino-6,7-dimethoxy-4(3H)-quinazolinone (22).—2-Chloro-6,7-dimethoxy-4(3H)-quinazolinone (7.2 g) in 70 ml of EtOH was heated in a pressure bottle with 50 ml of isopropylamine to 130° and kept at that temperature for 18 hr. The solution was then cooled. The liquids were evaporated, and the residue was chromatographed on a column of Florisil (340 g). Elution with a mixture of $CHCl_3$–EtOAc afforded 4.7 g of crystalline material which was recrystallized from MeOH to give 3.42 g of **22**.

For preparation of the **hydrochloride**, the free base was dissolved in 1 *N* HCl, and the solution was evaporated *in vacuo*.

Anal. ($C_{13}H_{17}N_3O_3 \cdot HCl$) C, H, N, Cl.

2-Diethylamino-6,7-dihydroxy-4(3H)-quinazolinone (47).—To 5 g of **6** was added 100 ml of 48% HBr, and the mixture was refluxed for 3 hr. The solution was chilled and the precipitate was filtered, washed with Et_2O, and dried to give 5.3 g of a solid which was recrystallized from EtOH–$(i\text{-Pr})_2O$ to furnish 4.1 g of **47**·HBr, mp 319–320°.

Anal. ($C_{12}H_{15}N_3O_3 \cdot HBr$) C, H, N, Br.

The hydrobromide (4 g) was dissolved in warm H_2O, the pH of the solution was adjusted to 7 with $NaHCO_3$ solution, and the precipitate was filtered to give 2.12 g of **47**. Recrystallization from 1 *N* HCl furnished the **hydrochloride**, mp 304–306°. *Anal.* ($C_{12}H_{15}N_3O_3 \cdot HCl \cdot 0.5H_2O$) C, H, N, Cl.

3-Methyl-6,7-dimethoxy-2,4(1H,3H)-quinazolinedione.—To 25 g of CH_3NCO in 100 ml of pyridine at 0° was added a cold solution of 27 g (0.28 mole) of methyl 6-aminoveratrate in 150 ml of pyridine. The solution was stirred at 0° for 30 min, then kept at room temperature for 1 hr, and concentrated to dryness. The crystalline residue was dissolved in 630 ml of 1 *N* NaOH (4:1, MeOH–H_2O) and refluxed for 2 hr. After evaporation of the solvent, the crystalline cake was dissolved in H_2O, the solution was acidified with AcOH, and the precipitate was filtered and recrystallized from DMF–H_2O to afford 29.1 g (93%) of product, mp 296–298°. *Anal.* ($C_{11}H_{12}N_2O_4$) C, H, N.

3-*o*-Tolyl-6,7-dimethoxy-2,4(1H,3H)-quinazolinedione was prepared similarly from 6-aminoveratrate and *o*-tolyl isocyanate in 94% yield, mp 281–283° (DMF–H_2O). *Anal.* ($C_{17}H_{16}N_2O_4$) C, H, N.

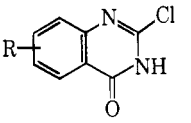
2-Chloro-3-methyl-6,7-dimethoxy-4(3H)-quinazolinone.—A mixture of 3-methyl-6,7-dimethoxy-2,4(1H,3H)-quinazolinedione (10.0 g) and 65 ml of $POCl_3$ was refluxed for 18 hr. The excess $POCl_3$ was removed *in vacuo*, the resulting crystalline residue was triturated in 400 ml of ice–H_2O, and the solids were collected to yield 9.42 g of crude material, mp 196–214°,[22] which was used in the next step without purification.

2-Chloro-3-(*o*-tolyl)-6,7-dimethoxy-4(3H)-quinazolinone.—The quinazolinedione (25 g) was refluxed in 350 ml of $POCl_3$ for 35 hr. Removal of the $POCl_3$ furnished a crystalline residue which was quenched with 1 l. of H_2O and filtered to afford 26 g of crude 2-chloro compound, mp 203–240°, which was used in the next step.

2-Diethylamino-3-methyl-6,7-dimethoxy-4(3H)-quinazolinone (52).—A slurry of 2-chloro-3-methyl-6,7-dimethoxy-4(3H)-quinazolinone (8 g) in 90 ml of EtOH and 30 ml of Et_2NH was transferred to a pressure bottle and heated to 130°. After 3 hr at 130°, the solution was cooled and concentrated, and the residue was triturated with 100 ml of H_2O. Filtration of the solids afforded 6.8 g of crystalline material which was recrystallized from hot EtOAc to afford 3.9 g (43%) of **52**, mp 126–129°. Two

TABLE IV

2-CHLORO-4(3H)-QUINAZOLINONES



R	Yield, %	Mp, °C
6-Cl	86	222–225
7-Cl	97	219–224
6-OCH_3	50	232–235[a]
7-OCH_3	98	231–233[a]
8-OCH_3	97	188–193
6,7-OCH_2O	98	274–275
6,7-OCH_2CH_2O	74	271–272
6,7-OC_2H_5	92	246–249
6,7-$OCH(CH_3)_2$	71	201–203
6,7-CH_3	87	239–240

[a] Recrystallized from DMF–H_2O.

more recrystallizations [from EtOAc–$(i\text{-Pr})_2O$, then MeOH–H_2O] gave the analytical sample: λ_{max} 247, 289, 320 mμ (ε 37,400, 12,800, 4780); nmr absorption of τ 2.42 (singlet, assigned to proton in position 5), 3.02 (singlet, proton in position 8), 6.0 (singlet, 6 protons of 6,7-OCH_3), 6.58 (singlet, 3 protons of 3-CH_3), 6.75 (quartet, 4 CH_2 protons of $-N(CH_2CH_3)_2$), and 8.83 (triplet, 6 CH_3 protons of $-N(CH_2CH_3)_2$).

4,5-Dimethoxy-N-carboxyanthranilic Anhydride.—The procedure followed was analogous to that described by Wagner and Fegley[35] for the preparation of N-carboxyanthranilic anhydride, except that the product was recrystallized from DMF: yield 41%, mp 274–275°. *Anal.* ($C_{10}H_9NO_5$) C, H, N.

3-Dimethylamino-6,7-dimethoxy-4(3H)-quinazolinone (54).—To a suspension of 13.2 g of 4,5-dimethoxy-N-carboxyanthranilic anhydride in 450 ml of $CHCl_3$ was added 30 ml of Me_2NNH_2, and the mixture was refluxed to complete solution (approximately 1 hr). The solvent was evaporated, and the resulting oily residue was crystallized by trituration in ethanolic HCl. The crystals (11.4 g, mp 231–233°) were dissolved in H_2O, and the solution was made basic with K_2CO_3 solution. Extraction with $CHCl_3$ afforded 9.1 g of an oily residue which was dissolved in 40 ml of HCOOH. This solution was refluxed for 18 hr and concentrated to dryness. The residue was suspended in H_2O, and the solid material was filtered to give 7.7 g of **54**, λ_{max} 242, 286, 308, 319 mμ (ε 70,700, 6110, 5420, 4250).

3-(N-Homopiperidinyl)-6,7-dimethoxy-4(3H)-quinazolinone (57).—4,5-Dimethoxy-N-carboxyanthranilic anhydride (6.69 g, 0.03 mole) and 9.09 g (0.09 mole) of N-aminohomopiperidine were dissolved in 50 ml of DMF, and the solution was warmed to 70°. After 3 hr, the DMF was removed, 80 ml of H_2O was added, and the crystalline solids were filtered. Recrystallization from MeOH–H_2O furnished 4.7 g of crystalline hydrazide, mp 146–147°, which was dissolved in 30 ml of HCOOH. After boiling at reflux for 1 hr, the solution was concentrated to give a crystalline residue which was triturated with H_2O, filtered, and dried. Recrystallization from EtOH afforded 3.4 g of **57**.

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Notes

Some New 3-Amino-2H-1,2,4-benzothiadiazine 1,1-Dioxides

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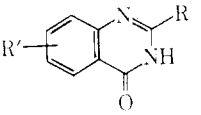
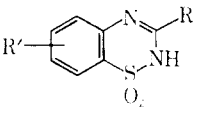
Several members of a series of amino-4(3H)-quinazolinones have been reported to cause antihypertensive effects when administered orally to conscious hypertensive dogs.[1] Particularly active were derivatives with methoxyl substitution in the 6 and 7 positions and dimethylamino, diethylamino, diallylamino, or N-methylpiperazino substitution in position 2 of the quinazoline ring system. These compounds (**1**) bear structural resemblances to certain 3-amino-2H-1,2,4-benzothiadiazine 1,1-dioxides (**2**),[2] which have been reported by others[3] to have hypotensive activity in anesthetized rats. However, in contrast to our observations with the 2-amino-4(3H)-quinazolinone (**1**) series, an unsubstituted amino group (R = NH_2) together with halogen substitution in the aromatic moiety or a secondary amino group (R = NHC_2H_5, NHC_6H_5) appeared to be optimal for activity in **2**. It has also been demonstrated previously that halogen substitution is advantageous for hypotensive activity in the related 3-alkyl-2H-1,2,4-benzothiadiazine 1,1-dioxides,[3,4] of which diazoxide (**2**, R = CH_3; R′ = 7-Cl) has attracted considerable interest, because it apparently lowers blood pressure by acting directly on the peripheral vasculature.[5]

In order to examine the effect of replacing the carbonyl function of the 2-amino-4(3H)-quinazolinones (**1**) with the isosteric sulfonyl moiety, or, alternatively, the effect of 6,7-dimethoxyl substitution in the 2H-1,2,-4-benzothiadiazines on antihypertensive activity, we have prepared the analogs **2** (R = dimethylamino, diethylamino, diallylamino, N-methylpiperazino; R′ = 6,7-OCH_3).



1



2

A suitable starting material was 4,5-dinitroveratrole (**3**)[6] (Scheme I). Reaction of **3** with aqueous sodium sulfite gave the sodium sulfonate **4**, which, without purification, was converted with thionyl chloride to the sulfonyl chloride **5**, in an over-all yield of 76%. Treatment of **5** with aqueous ammonia provided the sulfonamide (**6**) in 91% yield, which, upon reduction of the nitro group with stannous chloride, afforded **7** in 76% yield. The conversion of **7** to **8** was effected in the standard manner[7] by heating with urea. Attempts to chlorinate **8** in refluxing phosphorus oxychloride resulted only in the recovery of starting material.[8] Addition of N,N-dimethylaniline to the reaction mixture furnished the desired product, but

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(2) It may be noted that the 3 position in the 2H-1,2,4-benzothiadiazine 1,1-dioxides corresponds to the 2 position in the 4(3H)-quinazolinones.

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(4) J. G. Topliss, M. H. Sherlock, H. Reiman, L. M. Konzelman, E. P. Shapiro, B. W. Pettersen, H. Schneider, and N. Sperber, *J. Med. Chem.*, **6**, 122 (1963); B. A. Bierbaum, J. J. Traverso, and C. W. Whitehead, *ibid.*, **6**, 272 (1963); J. G. Topliss, L. M. Konzelman, E. P. Shapiro, N. Sperber, and F. E. Roth, *ibid.*, **7**, 269 (1964); N. Pisanti and F. Cresci Mutti, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 1003 (1964).

(5) A. A. Rubin, F. E. Roth, R. M. Taylor, and H. Rosenkilde, *J. Pharmacol. Exptl. Therap.*, **136**, 344 (1962); A. A. Rubin, L. Zitowitz, and L. Hausler, *ibid.*, **140**, 46 (1963); A. A. Rubin, *Angiology*, **14**, 74 (1963).

(6) J. Ehrlich and M. T. Bogert, *J. Org. Chem.*, **12**, 522 (1947).

(7) D. V. Parke and R. T. Williams, *J. Chem. Soc.*, 1760 (1950).

(8) Apparently, 3,4-dihydro-2H-3-oxo-1,2,4-benzothiadiazine 1,1-dioxides have not been halogenated previously.