94–95° (lit.[10] 96°), after two crystallizations from Et_2O–heptane (Darco).

6-Methoxyanthranilonitrile (IIIi).—*m*-Dinitrobenzene was converted into 2-methoxy-6-nitrobenzonitrile by reaction with KCN in refluxing aq MeOH.[24] Reduction of the nitro compd with $SnCl_2$ in HCl at 40–50° gave a 30% yield of IIIi, mp 141–143° (lit.[11] 141°) after several crystallizations with the aid of Darco, first from Et_2O–heptane, then from AcOH–H_2O, and finally from EtOH.

Synthesis of 2,4-Diaminoquinazolines. Reaction with Cyanamide (Method A). 2,4-Diamino-6-chloroquinazoline (IIe). An open pear-shaped flask containing a mixture of 0.5 g (0.00327 mole) of IIIf, 0.5 g (0.0119 mole) of crystalline cyanamide,[25] and 2.0 g (0.017 mole) of pyridine·HCl was immersed in an oil bath preheated to 180°. With the formation of a clear melt, the internal temp rose rapidly and reached a max of 164° before subsiding gradually. At 150° the flask was removed from the bath and allowed to cool. The partly resolidified melt was triturated with 10 ml of 95% EtOH until all the gummy material dissolved and only a yellow powder remained. The latter was filtered, washed with Et_2O in order to remove any unreacted IIIf, and digested with 30 ml of boiling H_2O. After removal of an insoluble residue, the filtrate was basified with 10% Na_2CO_3, and the gelatinous ppt was collected, washed dropwise with cold H_2O, and crystallized from H_2O (Darco); yield 0.27 g (37%). Two more crystallizations from H_2O (Darco) afforded analytically pure yellow needles, mp 269–271.5°.

Reaction with Cyanoguanidine (Method B). 2,4-Diamino-7-methoxyquinazoline (IIi).—A cold solution of 1.0 g (0.0067 mole) of IIIh in 40 ml of Et_2O was treated with dry HCl, and the ppt was collected, washed with Et_2O, and dried *in vacuo* to give 1.2 g (96%) of IIIh·HCl, mp 176–179°. An open pear-shaped flask containing a mixture of this material and 0.55 g (0.0065 mole) of cyanoguanidine was immersed in an oil bath preheated to 165°. The internal reaction temp was maintained at 158–164° for 10 min. The fused solid was dissolved in 25 ml of boiling H_2O, and the solution was cooled below 10° and basified with concd NaOH. The gummy yellow solid was filtered and washed with Et_2O to remove unreacted IIIh, and the residue was crystallized from 10 ml of H_2O (Darco); yield 0.38 g (31%), mp 230–231°. Repeated crystallization from H_2O furnished the analytical sample, yellow needles, mp 229–230°.

Reaction with Guanidine (Method C). 2,4-Diamino-7-chloroquinazoline (IIf).—To a solution of 0.37 g (0.0069 mole) of NaOMe in 12 ml of 2-methoxyethanol were added successively 0.63 g (0.0066 mole) of guanidine·HCl and 0.5 g (0.0033 mole) of IIIe. The mixture was refluxed with magnetic stirring for 71 hr. NaCl was removed from the hot reaction mixture by filtration and the filtrate was evapd to dryness under reduced pressure. The residue was triturated with 10 ml of Et_2O to remove unreacted starting material, IIIe. Crystallization of the Et_2O-insoluble residue from 35 ml of H_2O (Darco) afforded colorless needles, which were again triturated with 10 ml of Et_2O; yield 0.058 g (9%). An analytical sample, prepared separately *via* method A and crystallized 3 times from H_2O, melted at 229.5–230.5°.

(24) A. Russell and W. G. Tebbens, in "Organic Syntheses," 1st Ed., Vol. III, Wiley, New York, N. Y., 1955, p 293.

(25) We are grateful to the American Cyanamid Co., Bound Brook, N. J., for supplying us with a sample of crystalline cyanamide.

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Synthesis and Activity of Some 3-Aryl- and 3-Aralkyl-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamides

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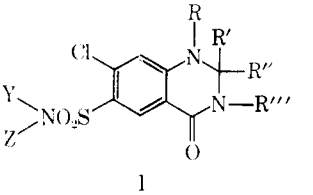
A series of 3-aryl- and 3-aralkyldi- and -tetrahydro-4-oxo-6-quinazolinesulfonamides have been synthesized and tested for pharmacological activity. Several of the compounds have been found to be potent diuretics.

The high biological activity of some benzothiadiazines[1] and 2-alkylquinazolinones[2] prompted us to investigate a series of 3-aryl and 3-aralkyl di- and tetrahydro-4-oxo-6-quinazolinesulfonamides. The compounds chosen for study are illustrated[3a] by the general formula I where R, R′, R″, Y, Z = H, alkyl, aryl, aralkyl, R‴ = aryl or aralkyl; R and R′ may also be absent (1,2-double bond).



1

The most interesting compounds, from a pharmacological point of view,[3b,c] were those in which the heterocyclic ring was saturated. So far the most promising of the compounds tested is 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide (metolazone) which is a potent, virtually nontoxic diuretic and natriuretic. The compounds were prepared in several ways; initially the unreduced precursors were reduced with $NaBH_4$–$AlCl_3$ mixture,[4] typical examples being illustrated in Scheme I.

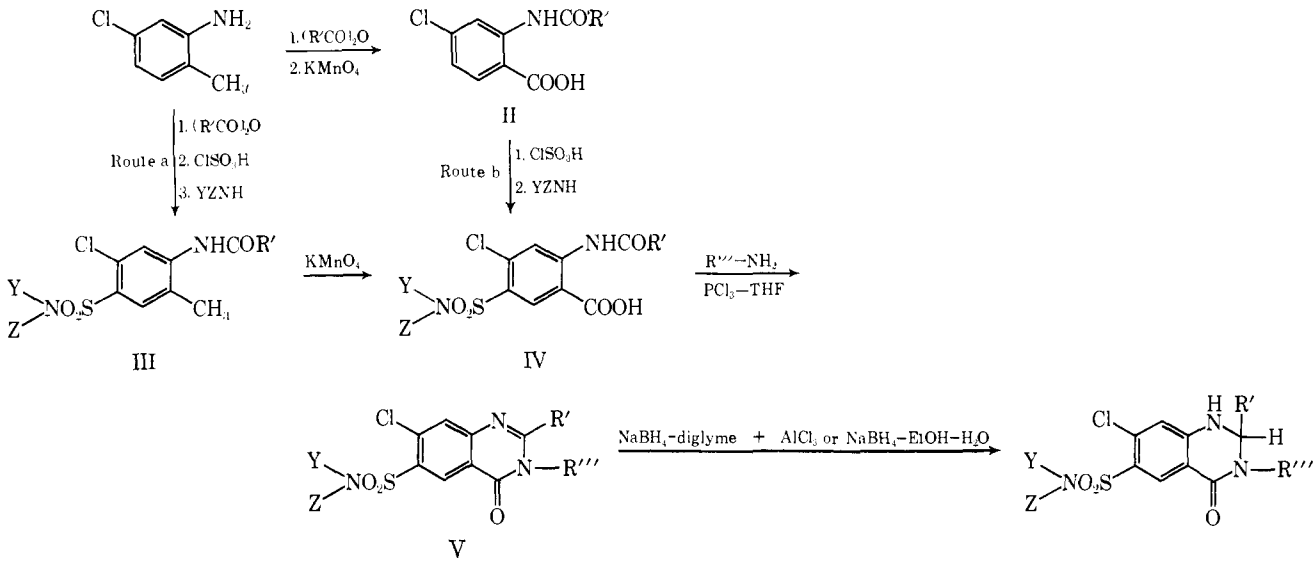
(1) K. H. Beyer and J. E. Baer, *Pharmacol. Rev.*, **13**, 517 (1961).

(2) (a) J. R. Cummings, L. M. Lipchuck, and E. H. Stokey, *Fed. Proc.*, **21**, 429 (1962); (b) R. H. Seller, M. Fuchs, G. Onesti, C. Swartz, A. N. Brest, and J. H. Moyer, *Clin. Pharmacol. Ther.*, **3**, 180 (1962).

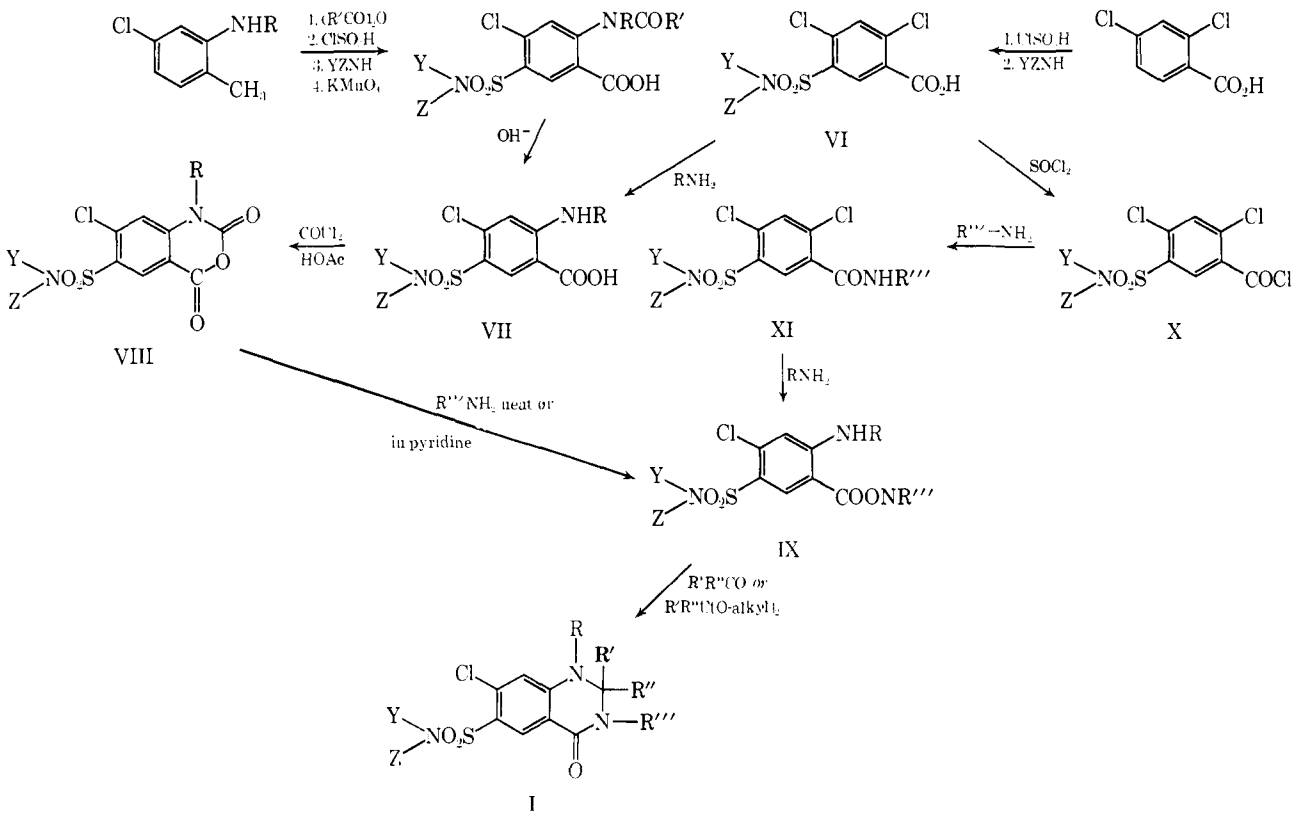
(3) (a) B. V. Shetty, U. S. Patent 3,360,518 (Dec 26, 1967); (b) E. J. Belair, *Pharmacologist*, **10**, 162 (1968); (c) E. Belair, F. Kaiser, B. Van-Deburg, A. Borrelli, R. Lawlor, R. Panasevitch, and J. Yelnosky, *Arch. Int. Pharmacodyn.*, **177**, 71 (1969).

(4) E. Cohen, B. Klarberg, J. R. Vaughan, *J. Amer. Chem. Soc.*, **82**, 2731 (1960).

SCHEME I



SCHEME II

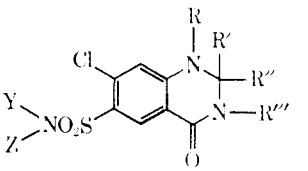


Route a in Scheme I gave the desired amido acid IV in reasonable yield when Y and Z = H, but when Y = CH_3, dealkylation occurred on oxidation of III. The *N*-methylsulfamyl compound could be obtained by route b, but the chlorosulfonation step proceeded in very poor yield (*ca.* 10%). The last two steps of Scheme I proved to be quite time consuming and gave only fair yields. Consequently other more satisfactory procedures were worked out. These are outlined in Scheme II.

The intermediate alkylamino acids VII in Scheme II were prepared most conveniently by chlorosulfonation of 2,4-dichlorobenzoic acid, treatment of the resulting sulfonyl chloride with cold aq amine to give the dichlorosulfamyl acid, and finally by heating this acid with the appropriate alkylamine, according to Sturm's procedure.[5] Two methods were used in the preparation of the amino amides IX. The appropriate isatoic anhydride VIII was treated with the desired amine, either neat or in pyridine solution, or the dichloroamide XI was treated with an excess of the amine at 60–100°. The latter reaction gave some replacement of the 4- as well as of the 2-Cl, but the impurity could usually be separated by recrystallization. The isatoic anhydrides VIII were prepared in almost quantitative yield by the

(5) K. Sturm, W. Siedel, R. Weyer, and H. Ruschig, *Chem. Ber.*, **99**, 328 (1966).

TABLE I
QUINAZOLINONE DERIVATIVES



Compd	R	R′	R″	R‴		Method and % yield
1	H	CH_3	H	2-$CH_3C_6H_4$	NH_2	E(81); L(80)
2	H	H	H	2-$CH_3C_6H_4$	NH_2	E(59); L(66)
3	H	C_2H_5	H	2-$CH_3C_6H_4$	NH_2	E(70); L(60)
4	H	C_6H_5	H	2-$CH_3C_6H_4$	NH_2	E(48)
5	H	CH_3	H	2-$CH_3C_6H_4$	$NHCH_3$	E(60); (56)[b]
6	H	CH_3	H	4-ClC_6H_4	NH_2	E(60); L(40)
7	H	CH_3	H	2-CH_3-3-ClC_6H_3	NH_2	M-I 0.5 hr (95)
8	H	CH_3	H	2-$CH_3C_6H_4CH_2$	NH_2	G(Δ5 min) (44)
9	H	*n*-C_3H_7	H	2-$CH_3C_6H_4$	NH_2	E(56)
10	H	*n*-C_4H_9	H	2-$CH_3C_6H_4$	NH_2	E(42)
11	H	$C_6H_5CH_2SCH_2$	H	2-$CH_3C_6H_4$	NH_2	F(56)
12	H	$CF_3CH_2SCH_2$	H	2-$CH_3C_6H_4$	NH_2	F(97)
13	H	$C_2H_5SCH_2$	H	2-$CH_3C_6H_4$	NH_2	F(51)
14	H	$ClCH_2$	H	2-$CH_3C_6H_4$	NH_2	F(95 amorphous 44 crystalline)
15	*c*	$ClCH_2$		2-$CH_3C_6H_4$	NH_2	K(44)
16	H	Cl_2CH	H	2-$CH_3C_6H_4$	NH_2	G(Δ2 min) (88)
17	H	$C_6H_5CH_2$	H	2-$CH_3C_6H_4$	NH_2	E(50)
18	H		H	2-$CH_3C_6H_4$	NH_2	F(40)
19	H		H	2-$CH_3C_6H_4$	NH_2	G(Δ30 min) (65)
20	H	CH_3	H	C_6H_5	NH_2	E(39)
21	H	$(CH_2)_5$		2-$CH_3C_6H_4$	NH_2	E(81)
22	H	CH_3	CH_3	2-$CH_3C_6H_4$	NH_2	E(91)
23	$C_6H_4CH_2$	CH_3	H	2-$CH_3C_6H_4$	$NHCH_3$	G(Δ60 min) (85)
24	H	ICH_2	H	2-$CH_3C_6H_4$	NH_2	F(75)
25	H	$Br(CH_2)_3$	H	2-$CH_3C_6H_4$	NH_2	E(98)
26	H	CH_2=$CHCH_2$	H	2-$CH_3C_6H_4$	NH_2	N(59)
27	*c*	CH_3		2-$CH_3C_6H_4$	NH_2	K(56)
28		C_2H_5		2-$CH_3C_6H_4$	NH_2	K(62)
29				2-$CH_3C_6H_4$	NH_2	K(75)
30	H	CH_3	H	2-$CF_3C_6H_4$	NH_2	L(78)
31		CH_3		2-$CF_3C_6H_4$	NH_2	K(75)
32	H	$(CH_2)_4$		2-$CH_3C_6H_4$	NH_2	G(Δ25 hr) (82)
33	H	CH_3	H	4-$CH_3C_6H_4$	NH_2	E(74)
34		CH_3		C_6H_5	NH_2	K(63)
35	H	CH_3	H	3-$CH_3C_6H_4$	NH_2	E(65)
36	H	$(CH_3)_2CH$	H	2-$CH_3C_6H_4$	NH_2	E(50)
37		CH_3		4-ClC_6H_4	NH_2	K(40)
38		CH_3		2-CH_3-3-ClC_6H_3	NH_2	K(82)
39	H	$(CH_2)_2N(CH_3)(CH_2)_2$		2-$CH_3C_6H_4$	NH_2	E(57) (sulfate)
40	H	CH_3OCH_2	H	2-$CH_3C_6H_4$	NH_2	G(Δ10 min) (20)
41	CH_3	CH_3	H	2-$CH_3C_6H_4$	NH_2	E(79)
42	H	CH_3	H	2,6-$(CH_3)_2C_6H_3$	NH_2	L(26)
43	H	CH_3	H	4-$NH_2SO_2C_6H_3$	NH_2	G[a](Δ3 hr) (50)
44	H	CH_3	CH_3	C_6H_5	NH_2	E(62)
45	H	$ClCH_2$	H	C_6H_5	NH_2	G(Δ2 min) (67)
46	H	CH_3	H	2-CH_3-4-HOC_6H_3	NH_2	E (55)

Recrystallization solvent	Mp, °C	Empirical formula	Analysis	Diuretic activity[a] Vol	Na	K
EtOH or *n*-BuOH	252–254	$C_{16}H_{16}ClN_3O_3S$	C, H, N, Cl, S	++++	++++	++++
EtOH	250–253.5	$C_{15}H_{14}ClN_3O_3S$	C, H, N, Cl, S	++++	++++	++++
EtOH	238–240	$C_{17}H_{18}ClN_3O_3S$	C, H, Cl, N, S	++	++	++
EtOAc–C_6H_{14} 4:1	241–243	$C_{21}H_{18}ClN_3O_3S$	C, H, Cl, N, S	++	+++	+++
EtOH	163–165	$C_{17}H_{18}ClN_3O_3S$	C, H, N	++	++	++
EtOH	316–318	$C_{15}H_{13}Cl_2N_3O_3S$	C, H, Cl, N, S	+	+	+
EtOH	264–267	$C_{16}H_{15}Cl_2N_3O_3S$	C, H, Cl, N, S	++	++	++
EtOH	234–235	$C_{17}H_{18}ClN_3O_3S$	C, H, Cl, N, S	−	+	+++
EtOH	221–224	$C_{18}H_{20}ClN_3O_3S$	C, H, Cl, N, S	++	++	++++
THF–C_6H_6 1:4	145–153	$C_{19}H_{22}ClN_3O_3S$	C, H, Cl, N, S	+	++	+++
EtOAc, then $MeOCH_2CH_2OH$	199–201	$C_{23}H_{22}ClN_3O_3S_2$	C, H, N, Cl, S	−	−	++
$CHCl_3$, then pptn from *i*-PrOH with Et_2O	147–150	$C_{18}H_{17}ClF_3N_3O_3S_2$	C, H, Cl, F, N, S	++++	++++	++++
EtOH	135–137	$C_{18}H_{20}ClN_3O_3S_2$	C, H, N, Cl, S	+	++	++
EtOH–H_2O 5:1	223–227	$C_{16}H_{15}Cl_2N_3O_3S$	C, H, N, Cl, S	++	++	+++
MeOH	256–258	$C_{16}H_{13}Cl_2N_3O_3S$	C, H, N, Cl, S	−	+	++
Dissolve in EtOAc, pptn with 2 vol of Et_2O	193–195	$C_{16}H_{14}Cl_3N_3O_3S$	C, H, Cl, N, S	++	++	++
EtOH	247–251	$C_{22}H_{20}ClN_3O_3S$	C, H, Cl, N, S	−	−	−
EtOAc digestion	163–166	$C_{21}H_{24}ClN_3O_3S$	C, H, Cl, N, S	+++	++	+
EtOH	238–240	$C_{19}H_{20}ClN_3O_3S$	C, H, Cl, N, S	+	+	+
EtOH	216–218	$C_{15}H_{14}ClN_3O_3S$	C, H, Cl, N, S	+++	+++	+++
DMF–H_2O 2:1	291–293	$C_{20}H_{22}ClN_3O_3S$	C, H, N, Cl, S	−	−	−
	261–263	$C_{17}H_{18}ClN_3O_3S$	C, H, N, Cl, S	+	+	+++
	163–165	$C_{24}H_{24}ClN_3O_3S$	C, H, Cl, N, S	+	+	+
$CH_3OCH_2CH_2OH$–H_2O 2:1	204–205	$C_{16}H_{15}ClN_3O_3S$	C, H, N[d]			
	140–155 amorphous	$C_{18}H_{19}BrClN_3O_3S$	*e*			
$HOCH_2CH_2OH$	281–283	$C_{18}H_{18}ClN_3O_3S$	C, H, N, Cl, S	+	+	+
EtOH	271.5–274[f]	$C_{16}H_{14}ClN_3O_3S$	C, H, N, Cl, S	+	+	+
EtOH	258–260	$C_{17}H_{16}ClN_3O_3S$	C, H, N, Cl, S	−	−	−
CH_3OH	241–243	$C_{20}H_{20}ClN_3O_3S$	C, H, N, Cl, S	+	+	+
EtOH	305–307	$C_{16}H_{13}ClN_3F_3O_3S$	C, H, N, Cl, F, S	++++	++++	+++
Digested with THF, then with C_6H_5	269–273	$C_{16}H_{11}ClF_3N_3O_3S$	C, H, Cl, N, F, S	+	+	++
EtOH	134–135	$C_{19}H_{20}ClN_3O_3S$	C, H, Cl, N, S	−	−	−
EtOH	302–303.5	$C_{16}H_{16}ClN_3O_3S$	C, H, Cl, N, S	++++	++++	+++
EtOH	257–260[f,g]	$C_{15}H_{12}ClN_3O_3S$	C, H, Cl, N, S	−	−	+++
EtOAc	232–234	$C_{16}H_{16}ClN_3O_3S$	C, H, N, Cl, S	+	+	+++
EtOH	222–236	$C_{18}H_{20}ClN_3O_3S$	C, H, N, Cl, S	++++	++++	++
HOAc	345–347[f]	$C_{15}H_{11}Cl_2N_3O_3S$	C, H, N, Cl, S			
Digested with hot CH_3OH	294–295	$C_{16}H_{13}Cl_2N_3O_3S$	C, H, N, Cl, S	+	+	+
H_2O	257 dec	$C_{20}H_{23}ClN_4O_3S$	C, H, N, Cl, S	−	−	−
EtOH	148–151	$C_{17}H_{18}ClN_3O_4S$	C, H, Cl, N, S	+++	+++	+++
	261–263	$C_{17}H_{18}ClN_3O_3S$	C, H, N, Cl, S	++++	++++	+++
EtOH	273–276	$C_{17}H_{18}ClN_3O_3S$	C, H, N, Cl, S	+++	+++	+++
$CH_3OCH_2CH_2OH$–$CHCl_3$ 3:1	257–259 dec	$C_{15}H_{15}ClN_4O_5S_2$	C, H, N, Cl, S	+	+	+
CH_3OH	279–287	$C_{16}H_{16}ClN_3O_3S$	C, H, Cl, N, S	−	−	−
EtOH	205–210	$C_{15}H_{13}Cl_2N_3SO_3$	C, H, Cl, N, S	++	++	+++
$HOCH_2CH_2OH$	305–306	$C_{16}H_{16}ClN_3O_4S$	C, H, N, Cl, S	++++	+++	++++

TABLE I (Continued)

Compd	R	R'	R''	R'''	Z	Method and % yield
47	H	CH_3	H	2-CH_3-4-CH_3O-C_6H_4	NH_2	E(57)
48	H	H	H	2-$C_2H_5C_6H_4$	NH_2	E(40)
49	CH_3	H	H	2-$CH_3C_6H_4$	NH_2	E(58)
50	$C_6H_5CH_2$	CH_3	H	2-$CH_3C_6H_4$	NH_2	E(57)
51	H	H	H	2,4,5-$(CH_3)_3C_6H_2$	NH_2	E(10)[c]
52	H	CH_3	H	2-$CH_3C_6H_4$	$NHCOCH_3$	(63)[d]
53	H	C_2H_5	H	2-$CH_3C_6H_4$	NH_2	E(47); H(72)
54	H	$C_6H_4CH_2OCH_2$	H	2-$CH_3C_6H_4$	NH_2	G(Δ10 min) (19)
55	H	$HOCH_2$	H	2-$CH_3C_6H_4$	NH_2	(80)[e]
56	$C_6H_5CH_2$	CH_3	H	2-$CH_3C_6H_4$	$N(CH_3)_2$	E(74)
57		CH_3		2,6-$(CH_3)_2C_6H_3$	NH_2	K(85)
58		H		2-$CH_3C_6H_4$	NH_2	K(53)
59	H		H	2-$CH_3C_6H_4$	NH_2	M(42)
60	H		CH_3	2-$CH_3C_6H_4$	NH_2	K(60)
61	H	CH_3	H	$C_6H_5CH_2$	NH_2	E(40)
62	H			2-$CH_3C_6H_4$	NH_2	A(65)
63	H	CH_3	H	2-$C_2H_5C_6H_4$	NH_2	E(60)
64	H	H	H	C_6H_5	NH_2	E(50)[f]
65	H	CH_3	H	2-$CH_3C_6H_4$	$N(CH_3)_2$	E(42)
66		$CHCl_2$		2-$CH_3C_6H_4$	NH_2	K(60)
67	H	CH_3	H	2-$HOCH_2C_6H_4$	NH_2	G(60)
68	$(CH_2)_2NMe_2$	CH_3	H	2-$CH_3C_6H_4$	NH_2	F(21)
69[a]	$C_6H_5CH_2$	H	CH_3	2-$CH_3C_6H_4$	$N(CH_3)_2$	E(65)
70	H	H			NH_2	E(85)[g]
71	H	H		2-CH_3CH_3	NH_2	F(21)[h]
72	CH_2CH_2OH	H	CH_3	2-$CH_3C_6H_4$	NH_2	F(34)[i]

[a] Diuretic activity: (−) very slight activity; (+) slight activity; (++) activity approximately equal to chlorothiazide; (+++) activity approximately equal to hydrochlorothiazide; (++++) activity greater than that of hydrochlorothiazide. [b] Catalytic debenzylation of 1-benzyl derivative with 5% Pd–C in MeOH at 60 psig. [c] When R and R'' = (−), the compound is unsaturated between the 1 and 2 position. [d] Product contained 11% of 2-bromomethyl compound. Analysis was correct for the mixture. [e] Product not analyzed since it was unstable, losing some HBr on standing or recrystallizing. Ir was in accord with structure. [f] Japanese patent 14021. [g] French patent 1509-M (1962). [h] The reaction was run in DMF under SO_2 instead of in AcOH. The solvent was evap-

action of an excess of $COCl_2$ on the arylamino acid VII in glacial HOAc. The dichloroamides XI were prepared in good yield by reaction of the acid chloride X with an excess of the desired amine at ambient temperature; usually little or no replacement of nuclear Cl occurs under these conditions.

The resulting aminoamides IX could be cyclized, in many cases, by both acid- and base-catalyzed addition of the appropriate carbonyl compound. However, the best results were consistently obtained with strong acid (*e.g.* H_2SO_4) catalysis in glacial HOAc, either at room temperature or at reflux, depending on the individual carbonyl compound or acetal. Acetals generally gave better results than aldehydes, while ketones worked better than ketals. Most of the aldehydes, ketones, and acetals reacted rapidly with the amino amides. The only exception was cyclopentanone, which required a much longer reaction time than did most of the other carbonyl compounds, including cyclohexanone.

An indirect method was generally used to make compounds with an unsaturated substituent in the 2 position (such as vinyl, allyl, propargyl, etc). The 2-allyl compound, for example, was readily prepared by dehydrohalogenating the 2-(3-bromopropyl) derivative with 1,5-diazabicyclo [4.3.0]-5-nonene.[6]

Nmr studies of some 2-alkyl-3-*o*-tolyl derivatives indicated that there is considerable steric interaction between the two substituents. 7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide has two doublets for the 2-Me group and two quartets for the 2-H group when the spectrum is run at room temperature. At 70° the doubling effect disappears and the expected doublet and quartet are observed. This temperature effect[7] is evidence for hindered rotation about the N aryl bond at the 3 position due to the steric intereaction of the *o*-Me and the 2-Me. Normal peaks are obtained for 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-phenyl-6-quinazolinesulfonamide where the absence of the *o*-Me permits free rotation of the Ph ring. 7-Chloro-1,2,3,4-tetrahydro-2,2-dimethyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide has two peaks for the geminal Me groups

(6) H. Oediger, H.-J. Kabbe, F. Moller, and K. Eiter, *Chem. Ber.*, **99**, 2012 (1966).

(7) T. H. Siddall and C. A. Prohaska, *J. Amer. Chem. Soc.*, **88**, 0172 (1966).

Recrystallization solvent	Mp, °C	Empirical formula	Analysis	Diuretic activity[a] Vol	Na	K
	229–230	$C_{17}H_{18}ClN_3O_4S$	C, H, Cl, N, S	+++	+++	+++
DMF–H_2O 2:1	283–287	$C_{16}H_{16}ClN_3O_3S$	C, H, Cl, N, S	++++	++++	++++
	202–204	$C_{16}H_{16}ClN_3O_3S$	C, H, N, Cl, S	++++	++++	++++
HOAc	193–195	$C_{23}H_{22}ClN_3O_3S$	C, H, N, Cl, S	++	+++	+++
EtOH	232–239	$C_{17}H_{18}ClN_3O_3S$	C, H, N, Cl, S	+++	+++	+++
Me_2CO–H_2O 2.5:1	243–246	$C_{18}H_{18}ClN_3O_4S$	C, H, N, Cl, S			
EtOH or $CHCl_3$	178–180	$C_{17}H_{18}ClN_3O_3S$	C, H, N, Cl, S	+++	+++	+++
EtOH	207–209	$C_{23}H_{22}ClN_3O_4S$	Cl, S			
EtOH	241–243	$C_{16}H_{16}ClN_3O_4S$	C, H, N, Cl	++	++	++
i-PrOH	183–184	$C_{25}H_{26}ClN_3O_3S$	C, H, N, S	++	++	++
EtOH	293–296	$C_{17}H_{16}ClN_3O_3S$	*p*	++	++	++
EtOH	278–282	$C_{15}H_{12}ClN_3O_3S$	C, H, N, S			
EtOH	268–270.5	$C_{20}H_{22}ClN_3O_3S$	C, H, N, Cl, S	–	–	–
i-PrOH	216–218	$C_{21}H_{24}ClN_3O_3S$	C, H, N, Cl, S	+	+	–
95% EtOH	216–218	$C_{16}H_{16}ClN_3O_3S$	C, H, N, Cl, S	++	++	+
PPtn from THF with EtOAc		$C_{15}H_{12}ClN_3O_4S$	C, H, N, Cl, S	++	++	+++
95% EtOH	270–275 dec	$C_{17}H_{18}ClN_3O_3S$	C, H, N, Cl, S	+	+	+
95% EtOH	283–290 dec	$C_{14}H_{12}ClN_3O_3S$	C, H, N, Cl, S			
95% EtOH	250–253 dec	$C_{18}H_{20}ClN_3O_3S$	C, H, Cl, N, S	++	++	++
95% EtOH	248–249 dec	$C_{16}H_{12}Cl_3N_3O_3S$	C, H, N, Cl, S	+	+	+
95% EtOH	238–240	$C_{16}H_{16}ClN_3O_4S$	C, H, Cl, N, S	++	++	++
95% EtOH	289–291	$C_{20}H_{23}ClN_4O_3S \cdot HCl$	C, H, Cl, N, S	+	+	+
95% EtOH	216–219	$C_{31}H_{34}N_4O_3S$	C, H, N, S	–	–	–
DMF–H_2O	262–267	$C_{15}H_{15}ClN_4O_3S$	C, H, Cl, N, S	++	++	++
i-PrOH	241–245	$C_{21}H_{25}ClN_4O_3S \cdot H_2SO_4$	C, H, Cl, N, S	++	++	++
95% EtOH	163–165	$C_{18}H_{20}ClN_3O_4S$	C, H, Cl, N, S			

orated and the thick oil was chromatographed on SiO_2 using 25% DMF in $CHCl_3$ as eluent. [i] Crude reaction product chromatographed on silica using 20% DMF in Et_2O. [j] Made by acylation of sulfamyl compound with Ac_2O in pyridine at room temperature for 6 hr. [k] Catalytic debenzylation of 2-benzyloxymethyl derivative with 5% Pd-C in THF at 4.2 kg/cm². [l] Chromatographed on SiO_2 using 15% DMF in Et_2O as eluent. [m] Ring closure in DMF instead of AcOH. [n] 6-Cl replaced by $PhCH_2$. [p] Not analyzed; ir in accord with structure.

which must be nonequivalent. The nonequivalence is due to the restricted rotation of the *o*-tolyl group.[8]

The activities of the compounds synthesized in this study, as well as their methods of preparation, are indicated in Tables I–III.

Pharmacology.—The diuretic and saluretic effects of each of the compounds listed in Table I were assayed by the method of Lipschitz, *et al.*[9] Male Sprague–Dawley rats, weighing 125–250 g were used. The animals were allowed to equilibrate for at least a week in their new environment before they were used in an assay. During this time they were maintained on Purina Laboratory Chow Checkers. Food, but not H_2O, was withdrawn 18 hr prior to testing. The animals were placed in HNO_3-washed, distilled-H_2O-rinsed, stainless steel metabolism cages for urine collection following compound and/or vehicle administration. In these experiments 4 or 5 animals per dose and control, housed individually in small stainless steel metabolism cages, were used. Urine was collected under light mineral oil for 5 hr. Urine volume was measured, Na^+ and K^+ concentrations were determined with a Perkin-Elmer Model 303 atomic absorption spectrophotometer, and Cl^- was measured with a Buchler-Cotlove chloridometer.

The reference compound for the early series of experiments was hydrochlorothiazide, and the doses for both reference and test compounds were 0.1, 1, 10, and 100 mg/kg of body weight. After 7-chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide had been well characterized and chosen for clinical studies, it was used as the reference compound at doses of 0.032, 0.1, and 0.32 mg/kg. In these experiments test compounds were administered at 0.1, 1, and 10 mg/kg.

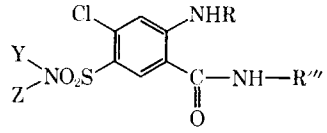
Test compounds and/or vehicle were administered by oral intubation. Compounds soluble in 2%, or less, of 0.2 *N* NaOH were administered in this vehicle, 0.5 ml/100 g of body weight. Those compounds not soluble in 0.2 *N* NaOH were suspended in 4% pregelatinized food-grade starch. All animals were saline-loaded by the oral route at the time of dosing with 2.5 ml of 0.9% saline/100 g of body weight.

(8) Lawrence Colebrook, Chemistry Department, University of Rochester, Rochester, N. Y., personal communication.

(9) W. L. Lipschitz, Z. Hadidian, and A. Kerpesar, *J. Pharmacol. Exp. Ther.*, **79**, 97 (1943).

TABLE II

Aminoamides



Compd	R	R'''	Y, Z	Method and % yield	Recrystallization solvent	Mp, °C	Empirical formula	Analysis	Diuretic activity[a] Vol	Na	K
73	H	2-$CH_3C_6H_4$	NH_2	B(64); C(59)	DMF–H_2O 5:3	292–294.5	$C_{14}H_{14}ClN_3O_3S$	C, H, N, Cl, S	–	–	–
74	CH_3	2-$CH_3C_6H_4$	NH_2	C(37); D(96)[b]	DMF–H_2O 5:3	274–275	$C_{15}H_{16}ClN_3O_3S$	C, H, N, Cl, S	++	++	++
75	$C_6H_5CH_2$	2-$CH_3C_6H_4$	NH_2	B(48)	EtOH–H_2O 2.5:1	225–227	$C_{21}H_{20}ClN_3O_3S$	Cl			
76	H	4-ClC_6H_4	NH_2	C(85)	EtOH–H_2O 2.5:1	203–205	$C_{13}H_{11}Cl_2N_3O_3S$	*f*			
77	H	2-CH_3-4-HOC_6H_3	NH_2	C(42)	*i*-PrOH	287–289	$C_{14}H_{14}ClN_3O_4S$	C, H, N, Cl, S			
78	H	2-$CH_3C_6H_4CH_2$	NH_2	C(70)	Digested with hot EtOH	275–278	$C_{15}H_{16}ClN_3O_3S$	C, H, Cl, N[g]			
79	H	2-CH_3-3-ClC_6H_3	NH_2	C(80)	EtOH	236–239	$C_{14}H_{13}Cl_2N_3O_3S$	*f*			
80	H	2-CH_3-4-$CH_3OC_6H_3$	NH_2	C(50)	DMF-H_2O 5:3	242–244	$C_{15}H_{16}ClN_3O_4S$	H, N, Cl, C[g]			
81	H	2-NH_2SO_2-5-ClC_6H_2	NH_2	B(Δ15 min) (15)[c,d]	$CH_3OCH_2CH_2OH$–$CHCl_3$	295–297 dec	$C_{13}H_{12}ClN_4O_5S_2$	C, H, N, Cl, S	–	–	–
82	H	2-$NH_2SO_2C_6H_4$	NH_2	B(Δ15 min) (24)[c,e]	$CH_3OCH_2CH_2OH$-Et_2O–C_6H_{14}	316–318 dec	$C_{13}H_{13}ClN_4O_5S_2$	C, H, N, Cl, S			
83	H	C_6H_5	NH_2	B(65)	DMF–H_2O 5:4	227–230	$C_{17}H_{12}ClN_3O_3S$	C, H, N, Cl, S			
84	H	$C_6H_5CH_2$	NH_2	C(64)	DMF–H_2O 5:4	Solvate 115–150	$C_{14}H_{14}ClN_3O_3S$	C, H, N, Cl, S			
85	$C_6H_5CH_2$	2-$CH_3C_6H_4$	$NHCH_3$	B(80); D(50)		225–227	$C_{22}H_{22}ClN_3O_3S$	C, H, N, Cl, S			
86	H	2-$C_2H_5C_6H_4$	NH_2	B(48)	Digested with hot CH_3OH	260–262	$C_{15}H_{16}ClN_3O_3S$	C, H, N, Cl, S			
87	H	2,4,5-$(CH_3)_3C_6H_2$	NH_2	C(38)	DMF–H_2O 1:1	278–287	$C_{16}H_{18}ClN_3O_3S$	C, H, N, Cl, S			
88	H	4-$CH_3C_6H_4$	NH_2	B(76)	DMF–H_2O5:4	260.5–263.5	$C_{14}H_{14}ClN_3O_3S$	C, H, N, Cl, S	–	–	–
89	H	2-$CH_3C_6H_4$	NH_2	B(93)		274–277	$C_{14}H_{14}ClN_3O_3S$	C, H, N, Cl, S	+	+	+++
90	$C_6H_5CH_2$	2-$CH_3C_6H_4$	$N(CH_3)_2$	D(42)	EtOH	233–235	$C_{23}H_{24}ClN_3O_3S$	Cl, S			
91	$(CH_3)_2N$ not RHN	2-$CH_3C_6H_4$	NH_2	R(25)	*n*-PrOH	182–184	$C_{16}H_{18}ClN_3O_3S$	C, H, N, Cl, S	+	+	+
92	H	2-$C_2H_5O_2CC_6H_4$	NH_2	B(85)	Digested with Me_2CO	262–266	$C_{15}H_{14}ClN_3O_3S$	C, H, N, Cl, S			
93	H	2-$HOCH_2C_6H_4$	NH_2	M(55)[h]	95% EtOH	223–225	$C_{14}H_{14}ClN_3O_4S$	C, H, Cl, N, S	–	–	–
94	$(CH_2)_2NMe_2$	2-$CH_3C_6H_4$	NH_2	D(24)	*i*-PrOH–H_2O	216–219	$C_{18}H_{23}ClN_4O_3S$	C, H, Cl, N, S	+	+	+
95	CH_3CO	2-$CH_3C_6H_4$	NH_2	(65)	95% EtOH	240–243	$C_{16}H_{16}ClN_3O_4S$	C, H, Cl, N, S			
96	H	2-Pyridyl	NH_2	B(27)	DMF–H_2O	208–211	$C_{12}H_{11}ClN_4O_3S$	C, H, Cl, N, S	–	–	–
97	H	6-Me-2-pyridyl	NH_2	S(16)	95% EtOH	188–191	$C_{13}H_{13}ClN_4O_3S \cdot HCl$	C, H, Cl, N, S	–	–	–
98	CH_3	2-Pyridyl	NH_2	B(27)[h]	95% EtOH	205–207	$C_{13}H_{13}ClN_4O_3S$	C, H, Cl, N, S	+	+	+

[a] Diuretic activity: (–) very slight activity; (+) slight activity; (++) activity approximately equal to chlorothiazide; (+++) activity approximately equal to hydrochlorothiazide; (++++) activity greater than that of hydrochlorothiazide. [b] Contaminated with a small amount of 2,4-di(methylamino) compound which is difficult to remove. [c] The aminobenzenesulfonamide was preheated to 195° under SO_2 and the solution was added to enough hot H_2O to dissolve the solvent and upon cooling precipitate the product. [d] Chromatographed on SiO_2 using 5% AcOH plus 10% DMF in $CHCl_3$. [e] Chromatographed on SiO_2 using 25% DMF in $CHCl_3$. [f] Not analyzed, ir is in accord with structure. [g] Reduction of **92** with $NaBH_4$–THF. [h] Chromatographed on SiO_2 using 15% DMF in Et_2O. [i] N: calcd 11.88, found 12.44. [j] C: calcd 48.72, found 48.19.

TABLE III

MISCELLANEOUS

Compd	R	R′	R″	Method and % yield	Recrystallization solvent	Mp, °C	Empirical formula	Analysis	Diuretic activity[a] Vol	Na	K
99	H_2NSO_2	$N(CH_3)_2$	COOH	P(61)	$CH_3OCH_2CH_2OH$	230–231	$C_9H_{11}N_2O_4SCl$	C, H, N, Cl, O, S	−	+	+
100	H_2NSO_2	NH—(CO—◇)	COOH	(95)[b]		260–262	$C_{13}H_{15}ClN_2O_5S$	Cl			
101	H_2NSO_2	$NHCOCH_3$	COOH	S(71)	95% EtOH	245–249[c]	$C_9H_9ClN_2O_5S$	C, H, N, Cl, S	+	+	+++
102	H_2NSO_2		$NHCO_2CO$	A(87)	Solu in THF, pptn with hexane	293–293.5	$C_8H_7ClN_2O_5S$	C, H, N, Cl, S			
103	CH_3NHSO_2		$C_6H_5CH_2NCO_2CO$	A(62)		235–238	$C_{16}H_{13}ClN_2O_4S$	Cl, S			
104	H_2NSO_2		$MeNCO_2CO$	A(91)	DMF–H_2O	292–296	$C_9H_7ClN_2O_5S$	C, H, N, Cl, S			
105	H_2NSO_2		$C_6H_{11}CH_2NCO_2CO$	A(83)		234–236	$C_{15}H_{11}ClN_2O_5S$	C, H, N, Cl			
106	H_2NSO_2	$NHCOCH_3$	2-$CH_3C_6H_4NHCO$	(40)[d]	EtOH–H_2O 1:1	240–243	$C_{16}H_{16}ClN_3O_4S$	C, H, N, Cl, S	1	1	1
107	H_2NSO_2	NHCO—◇	COOH	(90)[e]		243–246	$C_{12}H_{13}N_2O_5SCl$	C, N, Cl			

[a] Diuretic activity: (−) very slight activity; (+) slight activity; (++) activity approximately equal to chlorothiazide; (+++) activity approximately equal to hydrochlorothiazide; (++++) activity greater than that of hydrochlorothiazide. [b] Acylation of the aminoacid with cyclopentanecarbonyl chloride in EtOAc at reflux for 5 hr. [c] French patent 1509-M (1962). [d] Made by acylation of the amino compound in Ac_2O at reflux for 15 min. [e] Same as *b* but with cyclobutanecarbonyl chloride.

Net changes in volume and ionic excretion compared to control were calculated and log dose–response curves were plotted for each parameter. Potency, on a weight basis, was compared by measuring the horizontal distance between the reference and test compound curves. Cl^- output has not been included in Table I since it invariably paralleled Na^+ output.

Structure–Activity Relationships. i. Diuretic and Natriuretic Activity.—All of the highly active compounds have at least one H in the 2 position, a primary SO_2NH_2 in the 6 position and an *ortho* or *para* lower alkyl- or CF_3-substituted aromatic ring in the 3 position of the quinazoline nucleus. The 1 substituent, and the other substituent in the 2 position, may be either H or Me; increasing the size of the substituent in either position reduces diuretic and natriuretic activity in proportion to the increase in group size. An exception to this trend is the 2-*i*-C_3H_7 derivative, which retains the activity of the 2-Me analog. Replacing both H's in the 2 position diminishes renotropic activity.

The presence of an electron-rich group α to the 2 position (*e.g.*, 2-CH_2OCH_3) causes a very substantial drop in diuretic and natriuretic effects except in the case of the 2-$CH_2SCH_2CF_3$ analog.

Removal of the *o*- or *p*-Me from the 3-aryl ring, changing it to the *meta* position, or adding other alkyl groups to the ring all cause decreased diuresis and natriuresis. Changing the Me group to a CH_2OR or replacing it with an electron-withdrawing group greatly reduces activity. Changing Me to Et has little effect if the 2 position is unsubstituted, but causes a substantial drop in renotropic effect with an alkyl group in the 2 position.

Separation of the aryl group in the 3 position from the quinazoline nucleus by an alkyl bridge results in reduced diuretic activity. Changing the primary SO_2NH_2 in the 6 position to either a secondary or tertiary amide reduces activity. Likewise, removal of the 7-Cl or replacement with an electron-donating group markedly reduces renotropic activity.

ii. Kaliuresis.—K^+ excretion generally parallels that of Na^+, the most notable exceptions occurring in the 2-Pr derivative. With the 2-*i*-Pr derivative increases in volume and Na^+ output were about the same as with the 2-Me analog, but the increase in K^+ output was much less. The 2-*n*-Pr analog, however, caused a high K^+ output accompanied by small increases in Na^+ and volume output.

It was generally true that the magnitude of natriuretic, diuretic, and kaliuretic activity decreased with increasing chain length; the rate of decrease in kaliuretic activity was slower than in natriuretic or diuretic activity. Increasing chain branching tended to cause a more rapid rate of decrease in kaliuresis than in natriuresis or diuresis.

Experimental Section

Melting points were determined using a Thomas-Hoover apparatus and are corrected. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical value.

5-Chloro-2-methyl-4-sulfamylacetanilide.—The procedure described here is a variation of that used by Cohen and coworkers.[4] 5-Chloro-2-methylacetanilide[4] (1200 g, 6.55 moles) was slowly added to 3823 g (32.8 moles) of $ClSO_3H$ at 20° with ice bath cooling. The bath was then removed and 352 g (6.0 moles) of NaCl

was slowly added (foams). The solution was then heated very slowly to 92° (vigorous foaming again occurred from 75 to 90°) with good stirring and held there 1 hr (temp above 90–95° cause extensive decomposition of the product). The hot, thick solution was poured into a mixture of 10 l. of Me_2CO and ice, with enough ice being added during the reaction mixture addition to keep the temp at *ca.* 0°. The white acid chloride was filtered off and washed with H_2O. A sample was dried and recrystd from Me_2CO, mp 185–187°.

The remainder of the damp cake was added to 7.5 l. of concd NH_4OH and stirred overnight. The solid was filtered off and dissolved in 8 l. of H_2O and 520 ml of 50% NaOH at room temp. The insoluble by-products were filtered off and the filtrate was acidified with concd HCl (to pH 1–2). The product was filtered off (slow filtration due to fine particle size), washed neutral with H_2O, and dried to yield 888 g (52%) of product, mp 267.5–270°.

4-Chloro-5-sulfamyl-*N*-acetylanthranilic Acid.—This procedure is also a variation of that used by Cohen, *et al.*,[4] and gives approximately double their yield of product. To a hot (80°) solution of 366 g (1.482 mole) of $MgSO_4 \cdot 7H_2O$ (Epsom salts) in 2.8 l. of H_2O was added 130 g (0.50 mole) of powdered 5-chloro-2-methyl-4-sulfamylacetanilide. With stirring and maintaining the temp at *ca.* 83°, 234 g (1.48 mole) of $KMnO_4$ was added portionwise over a period of 2 hr. The mixture was then kept at *ca.* 85° with stirring for an additional 3 hr. By this time the pink color of the permanganate had been discharged. The warm reaction mixture was filtered and the cake washed with H_2O. The filtrate was then slowly treated with concd HCl to pH 1–2. The product was filtered, washed with H_2O, and dried; yield, 103 g, mp 245–249° dec.

4-Chloro-5-sulfamylanthranilic acid was prepared from the acetylated acid using the method of Cohen, *et al.*,[4] for hydrolysis.

Isatoic Anhydrides (VIII).—The isatoic anhydrides were prepared in essentially quantitative yield by the action of $COCl_2$ on a slurry or solution of the corresponding amino acid in glacial AcOH.

Method A. Typical Example. 6-Chloro-7-sulfamylisatoic Anhydride.—4-Chloro-5-sulfamylanthranilic acid (250.7 g, 1 mole) was slurried in 2 l. of glacial AcOH and 200 g (2 moles) of liquified $COCl_2$ was added all at once. The mixture was stirred for 3 hr, filtered, washed with glacial AcOH, thoroughly washed with anhyd Et_2O, and then dried *in vacuo* over P_2O_5 and NaOH. The product weighed 263 g, mp 288–290°. It could be recrystd by dissolving in THF (20 ml/g) and adding *n*-hexane (180 ml/g), giving a 60% recovery, mp 293–293.5°.

Aminoamides (IX).—The aminoamides were prepared in 3 ways: the corresponding isatoic anhydride could be treated with a large excess of the appropriate amine at high temp (method B) or refluxed with a slight excess of the amine in pyridine (method C), or the 2-chloroamide could be reacted with the amine (method D).

Method B. Example. 2-Amino-4-chloro-5-sulfamyl-*N*-*o*-tolylbenzamide.—6-Chloro-7-sulfamylisatoic anhydride (720 g, 2.60 moles) was added to 4.2 l. of freshly distilled *o*-toluidine and the mixture was heated as rapidly as possible under N_2 to 185°, held at this temp for 5 min, and then allowed to cool to about 30°. The resulting slurry could either be treated with 4.2 l. of Et_2O, immediately filtered, and washed with Et_2O, or poured into an excess of dilute HCl and ice, filtered, and washed with H_2O. In either case the solid was then slurried in 9000 ml of *i*-PrOH, filtered, washed with *i*-PrOH, slurried in dil NH_4OH, filtered, washed with H_2O, then with *i*-PrOH, and finally with Et_2O. The product is relatively insoluble in these solvents and almost all by-products were removed by this treatment. The weight of purified product was 560 g, mp 288–290°. The product could be recrystd by dissolving in DMF at 90° (2 ml/g) and adding boiling H_2O (1 ml/g). Recovery was about 80%.

Method C. 2-Amino-4-chloro-5-sulfamyl-*N*-(4-methoxy-2-methylphenyl)benzamide.—6-Chloro-7-sulfamylisatoic anhydride (27.7 g, 0.10 mole) was added to a mixture of 100 ml of pyridine and 41.1 g of freshly distilled 4-methoxy-2-methylaniline (0.3 mole) and the mixture was refluxed for 10 min. It was then allowed to cool to room temp, poured into dil HCl plus ice and the product purified as in method B. The weight of product was 23 g, mp 242–244°. The recovery on recrystallization as in method B was about 80%.

Method D. 2-Benzylamino-4-chloro-5-(*N*,*N*-dimethylsulfamyl)-*N*-*o*-tolylbenzamide.—2,4-Dichloro-5-(*N*,*N*-dimethylsulfamyl)-*N*-*o*-tolylbenzamide (38.7 g, 0.1 mole) was added to 200 ml of benzylamine, the mixture heated at 100° for 1 hr, then poured into H_2O, and the product filtered off and washed with H_2O. The crude product weighed 39 g. Recrystallization from EtOH (3 ml/g) yielded 19 g of product, mp 233–235°.

Cyclization Procedures. Intermolecular cyclization of the appropriate aminoamide and potential carbonyl compound to the 1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamide was brought about by 5 related procedures. These are: mineral acid catalyzed cyclization in cold glacial AcOH (method E); mineral acid catalyzed cyclization in hot (~100°) glacial AcOH for approx 1 min (method F), or for up to several hours (method G); and alkali-catalyzed cyclization in hot EtOH (method H). Some substituted 2-acylaminobenzamides were cyclized to the corresponding quinazolinones using PCl_5 and the appropriate amine in THF (method K).

Method E. Example. 7-Chloro-1,2,4,5-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide.—2-Amino-4-chloro-5-sulfamyl-*N*-*o*-tolylbenzamide (33.9 g, 0.1 mole) was slurried in 350 ml of glacial AcOH and 11.7 g (0.13 mole) of 1,1-dimethoxyethane was added, followed by 0.5 ml of concd H_2SO_4 or 2 ml of 30% aq HCl in glacial AcOH. The resulting slurry was stirred for 3 hr, during which time solution or noticeable thinning of the slurry occurred, followed by precipitation of the product. With some analogs, where solubility of the product in AcOH was appreciable, it was advantageous to add Et_2O (1–3 vol) to insure complete pptn of the product. The product was filtered off, washed with glacial AcOH and Et_2O, and dried *in vacuo* over P_2O_5, yielding 33 g of product, mp 252–254°. It could be recrystd from EtOH (2.5 ml/g for solution, followed by concentration to one-third volume) giving about 80% recovery. The product is polymorphic and melting points range from 218 to 259°; nmr (DMSO-d_6), 2-Me (↑8.57; 8.58, two doublets), 2-H (↑4.84; 4.46, two quartets).

Method F. 7-Chloro-2-chloromethyl-1,2,3,4-tetrahydro-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide.—2-Amino-4-chloro-5-sulfamyl-*N*-*o*-tolylbenzamide (17 g, 0.05 mole) slurried in 175 ml of glacial AcOH was heated to 100° and 8.5 g (0.07 mole) of 2-chloro-1,1-dimethoxyethane was added. After about 15 sec 0.5 ml of concd H_2SO_4 was added and the reaction mixture stirred for about 45 sec (solution occurred within 20 sec), then poured into 100 ml of H_2O with good stirring. The product was filtered off, washed neutral, and dried *in vacuo* over P_2O_5. The product (18.5 g) thus obtained was amorphous and melted at *ca.* 86°, though the indicated little, if any, impurities present. Recrystallization from EtOH or EtOAc gave 9.0 g of crystalline product, mp 221–223°.

Method G. 7-Chloro-2-dichloromethyl-1,2,3,4-tetrahydro-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide.—2-Amino-4-chloro-5-sulfamyl-*N*-*o*-tolylbenzamide (17 g, 0.05 mole) in 60 ml of glacial AcOH was treated with 18.7 g (0.1 mole) of 2,2-dichloro-1,1-diethoxyethane and 0.5 ml of concd H_2SO_4, refluxed for 5 min, cooled, and diluted with 90 ml of Et_2O. The product was filtered off and washed with Et_2O. After drying *in vacuo* over P_2O_5 there was obtained 17.6 g of product, mp 193–195°.

Method H. 7-Chloro-2-ethyl-1,2,3,4-tetrahydro-4-oxo-3-*m*-tolyl-6-quinazolinesulfonamide.—2-Amino-4-chloro-5-sulfamyl-*N*-*m*-tolylbenzamide (5 g, 0.0147 mole), 3 g (0.052 mole) of propionaldehyde, and 0.5 ml of 50% NaOH solution were added to 100 ml of 95% EtOH and refluxed for 24 hr. The reaction mixture was added to H_2O, acidified, and filtered to yield 4.5 g of product. Recrystallization from 95% EtOH gave 4 g of product, mp 178–180°.

Method K. 7-Chloro-2-cyclopentyl-3,4-dihydro-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide.—4-Chloro-5-sulfamyl-*N*-cyclopentylcarbonylanthranilic acid (13.5 g, 0.039 mole) was suspended in 500 ml of THF, 8 g (0.075 mole) of *o*-toluidine and 8 g (0.59 mole) of PCl_5 were added, and the mixture was refluxed for 4 hr and cooled. The product was filtered off, and after recrystn from 400 ml of MeOH weighed 13.8 g, mp 241–243°.

Reduction of 3,4-Dihydro-4-oxo-6-quinazolinesulfonamide Derivatives.—Two methods were used: the first one involved reduction in diglyme with $NaBH_4$–$AlCl_3$ combination (method L); the second, and by far the easier method, involved reduction with $NaBH_4$ alone in aq EtOH suspension at reflux from 4 to 24 hr, depending on the compound involved.

Method L. 7-Chloro-1,2,3,4-tetrahydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide. Anhydrous $AlCl_3$ (5.34 g, 0.04 mole) was added to 4 l. of diglyme and to the resulting solution was added 43.6 g (0.12 mole) of 7-chloro-3,4-dihydro-2-methyl-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide. A solution of 4.56 g

(0.12 mole) of $NaBH_4$ in 1 l. of diglyme was added portionwise over 1 hr with good stirring. The reaction mixture was then heated at 85° for 1 hr, cooled to 25° and the complex decomposed with 600 ml of H_2O and 100 ml of concd HCl. The solvent was removed at 60–70° under reduced pressure. The viscous residue was triturated with H_2O and the crude product which solidified was filtered and washed with H_2O. After two recrystns from EtOH the product weighed 36.5 g, mp 253–259°.

Method M. 7-Chloro-3-(3-chloro-2-methylphenyl)-1,-2,3,4-tetrahydro-2-methyl-4-oxo-6-quinazolinesulfonamide.—7-Chloro-3-(3-chloro-2-methylphenyl)-3,4-dihydro-2-methyl-4-oxo-6-quinazolinesulfonamide (2.2 g, 0.006 mole) was suspended in 60 ml of EtOH and 20 ml of H_2O. $NaBH_4$ (2 g, 0.035 mole) was added under N_2 and the mixture was stirred for 10 min. It was then refluxed for 1.5 hr, poured into 500 ml of H_2O, and acidified with HCl. The crude product was filtered off and recrystd from 60 ml of absolute EtOH to yield 2.1 g of product, mp 264–267°.

Miscellaneous Procedures. Method N. 2-Allyl-7-chloro-1,2,3,4-tetrahydro-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide.—2-(3-Bromopropyl)-7-chloro-1,2,3,4-tetrahydro-4-oxo-3-*o*-tolyl-6-quinazolinesulfonamide (2.4 g, 0.005 mole) in 12 ml of DMSO was treated with 0.63 g (0.0051 mole) of 1,5-diazabicyclo[4.3.0]-nonene[6] under N_2 and the solution stirred at ambient temp for 2 hr. The solution was poured into 100 ml of H_2O, acidified, filtered, washed (H_2O), and recrystd from 5 ml of ethylene glycol, yielding 1.2 g of product, mp 281–283°.

Method P. 4-Chloro-2-dimethylamino-5-sulfamylbenzoic Acid.—2,4-Dichloro-5-sulfamylbenzoic acid (54 g, 0.20 mole) was dissolved in 250 ml of concd NH_4OH. DMF (250 ml) was added and the solution heated in a pressure vessel at 140–145° (15.46 kg/cm²) for 6 hr. Most of the solvent was removed on a rotating evaporator under reduced pressure and 400 ml of H_2O was added to the residue. The product was filtered off, washed with H_2O, and dried. It weighed 45 g, mp 227–229°. Recrystallization from 2-methoxyethanol (6 ml/g) yielded 33 g of product, mp 230–231°.

Method R. 4-Chloro-2-dimethylamino-5-sulfamyl-*N*-*o*-tolylbenzamide.—4-Chloro-2-dimethylamino-5-sulfamylbenzoic acid (20.6 g, 0.074 mole) in 300 ml of THF was treated with 7.7 g (9.55 ml, 0.076 mole) of *N*-methylmorpholine and stirred for 30 min. The thick slurry was treated with 8.3 g (6.1 ml, 0.076 mole) of $ClCO_2C_2H_5$ and stirred for 10 min. *o*-Toluidine (9.4 g, 0.09 mole) was added and the mixture stirred at room temp for 70 hr. The solvent was then removed on the Rotovap, 200 ml of H_2O was added, and the solid was filtered off. This was slurried with dil $KHCO_3$, filtered, washed with H_2O, slurried with dil HCl, filtered, and again washed with H_2O. After drying *in vacuo* over P_2O_5 it weighed 5.7 g, mp 172–178°. It could be recrystd from PrOH (1.5 ml/g) to yield a product, mp 182–184°.

Method S. 2-Amino-4-chloro-5-sulfamyl-*N*-(3-methyl-2-pyridyl)benzamide.—4-Chloro-5-sulfamylanthranilic acid cyanomethyl ester (60 g, 0.207 mole) was added to 200 ml of freshly distilled 2-amino-3-methylpyridine and the mixture heated at 110°, under N_2 and with stirring, for 4 hr. The reaction mixture was then cooled and poured into 1 l. of H_2O with vigorous stirring. The aqueous layer was discarded and the oil again treated with 1 l. of H_2O. The aq layer was discarded and the oily residue was dissolved in 400 ml of 2.5 *N* HCl. After standing overnight the hydrochloride was filtered and washed (H_2O). It was then suspended in H_2O and treated with a saturated solution of $NaHCO_3$, with stirring, until a pH of 7 to 8 was reached. The product was filtered and recrystd from 95% EtOH, yield 11.2 g, mp 188–191°.

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Aminoalkenylbenzenesulfonamides with Hypotensive and Histamine-Releasing Properties

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A series of *p*- and *m*-sulfamoyl-substituted dialkylaminoalkylbenzhydrylidene derivatives were prepared and their pharmacological properties evaluated. The most active compound, *trans*-*N*,*N*-dimethyl-*p*-(3-dimethylamino-1-phenyl-1-propenyl)benzenesulfonamide (**15**), was found to cause prolonged blood pressure lowering in dogs with concomitant release of endogenous histamine on iv and oral administration.

A series of sulfamoyl-substituted benzhydrylidene derivatives of general structure D was prepared (Chart I and Table I). The corresponding unsubstituted benzhydrylidene derivatives (*e.g.*, **19**, Table I) had been reported to have anticholinergic and antihistaminic properties.[2] The compounds also represent "open" analogs of sulfamoyl-substituted tricyclic derivatives such as the phenothiazine derivative thioproperazine,[3] the thioxanthene derivative thiothixene,[4] and others.[5] Julou, *et al.*, reported that the 2-dimethylsulfamoyl-substituted promethazine, dimetiotazine, possesses pronounced antiserotonin activity in addition to the antihistaminic properties of the parent compound and clinical evaluation confirmed its effectiveness in treatment of migraine and vascular chronic headache.[6] Evaluation of several of the compounds

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