

## Diuretics. 3-Amino- and 3-Hydroxy-7-chloro-3,4-dihydro-4-oxo-6-quinazolinesulfonamides

MILTON L. HOEFLE AND ANN HOLMES

Research Laboratories, Parke, Davis and Company, Ann Arbor, Michigan 48106

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A series of 3-substituted-amino- and 3-hydroxy-7-chloro-3,4-dihydro-4-oxo-6-quinazolinesulfonamides was prepared and evaluated for diuretic activity. The introduction of an amino or a dimethylamino group in the 3 position had little effect, but the introduction of a hydroxyl group enhanced the activity. The corresponding 1,2,3,4-tetrahydro derivatives proved to be the most active compounds in this series.

In the course of investigating the diuretic activity of derivatives of 4-chloro-3-sulfamoylbenzoic acid it was found that the hydrazide and hydroxamic acid were among the most potent.<sup>1</sup> We considered it of interest to incorporate these structural features in a fused heterocyclic ring system as 3-amino- or 3-hydroxyquinazolone. The preparation and diuretic activity of such a series of 3-substituted quinazolones are described in this paper.

Cyanomethyl 4-chloro-3-sulfamoylanthranilate was prepared from 4-chloro-3-sulfamoylanthranilic acid. Treatment of this activated ester with hydrazine hydrate yielded the desired 4-chloro-5-sulfamoylanthranilic acid hydrazide (Ia). In view of our experience and that of other workers<sup>2</sup> with related compounds, it appeared advisable to block the free amino group of the hydrazide before attempting cyclization. Compound Ia was treated with acetone to yield the isopropylidene derivative (II) which was then cyclized by treatment with ethyl orthoformate to yield N-(7-chloro-3,4-dihydro-3-isopropylideneamino-4-oxo-6-quinazolinyloxy)sulfonylformimidic acid ethyl ester (III) (Scheme I). When III was dissolved in boiling water, hydrolysis occurred yielding the desired 3-amino-7-chloro-3,4-dihydro-4-oxo-6-quinazolinesulfonamide (Va). However, it was found to be simpler to reflux either Ia or II with formic acid for in both cases the product obtained was N-(7-chloro-4-oxo-6-sulfamoyl-3(4H)-quinazolinyloxy)formamide (IV). Compound IV was readily hydrolyzed with 2 N HCl to yield Va. More vigorous hydrolysis yielded the starting material (Ia). 3-Amino-7-chloro-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamide (VIa) was obtained by treating compound II with formaldehyde in dilute sulfuric acid.

4-Chloro-5-sulfamoylanthranilic acid 2,2-dimethylhydrazide (Ib) was most readily prepared by treating 4-chloro-5-sulfamoylanthranilic acid with N,N-dimethylhydrazine in the presence of N,N'-dicyclohexylcarbodiimide. Compound Ib was cyclized by refluxing in formic acid to yield 7-chloro-3-(dimethylamino)-3,4-dihydro-4-oxo-6-quinazolinesulfonamide (Vb). Similarly, 7-chloro-3-(dimethylamino)-1,2,3,4-tetrahydro-4-oxo-6-quinazolinesulfonamide (VIb) was obtained by the treatment of Ib with formaldehyde in ethanol containing a catalytic amount of HCl.

The synthesis of the corresponding 3-hydroxyquinazolinesulfonamides<sup>3</sup> was accomplished by utilizing

similar routes. Thus, cyanomethyl 4-chloro-5-sulfamoylanthranilate and aqueous hydroxylamine yielded 1-amino-4-chloro-5-sulfamoylbenzhydroxamic acid (VII). Compound VII (as the barium salt) cyclized on refluxing with formic acid to give 7-chloro-3,4-dihydro-3-hydroxy-4-oxo-6-quinazolinesulfonamide (VIII) (Scheme II). Treatment of the sodium salt of VIII with dimethyl sulfate yielded the corresponding 3-methoxy derivative (IX). The reduction of VIII with sodium borohydride-aluminum chloride in diglyme gave 7-chloro-1,2,3,4-tetrahydro-3-hydroxy-4-oxo-6-quinazolinesulfonamide (X).

4-Chloro-5-sulfamoylanthranilic acid and acetic anhydride were heated at reflux, and the resulting crude 7-chloro-2-methyl-4-oxo-4H-3,1-benzoxazine-6-sulfonamide was treated directly with an aqueous solution of hydroxylamine. The resulting solution was made strongly basic with sodium hydroxide and warmed to assure ring closure. Acidification yielded 7-chloro-3,4-dihydro-3-hydroxy-2-methyl-4-oxo-6-quinazolinesulfonamide (XI).

**Biological Results.**—These compounds were tested in both rats and dogs by methods which have been previously described.<sup>4</sup> The results in dogs are summarized in Table I where the data for a standard dose of 2.5 mg/kg is listed for the purpose of comparison.

The introduction of an amino substituent in the 3 position of the quinazoline ring had little effect upon the diuretic activity in this series in contrast to the marked effect that was noted in the case of the 4-chloro-3-sulfamoylbenzoic acid hydrazides.<sup>1</sup> However, the introduction of a hydroxyl group did lead to significantly enhanced activity. The increased potency of the 1,2,3,4-tetrahydro derivatives (VIa, VIb, IX) parallels the results in the series of quinazolones unsubstituted in the 3 position.<sup>5</sup>

### Experimental Section<sup>6</sup>

**4-Chloro-5-sulfamoylanthranilic Acid Cyanomethyl Ester.**—A solution of 50.0 g of 4-chloro-5-sulfamoylanthranilic acid<sup>5</sup> and 23.0 g of chloroacetonitrile in 400 ml of Me<sub>2</sub>CO was stirred at room temperature, and 42 ml of NEt<sub>3</sub> was added dropwise. The resulting solution was then heated at reflux for 24 hr. After cooling the Et<sub>3</sub>NH<sup>+</sup>Cl<sup>-</sup> was removed by filtration and the filtrate

(3) M. L. Hoefle, U. S. Patent 3,186,992 (1965).

(4) L. T. Blouin, D. H. Kaump, R. L. Fransway, and D. Williams, *J. New Drugs*, **3**, 302 (1963).

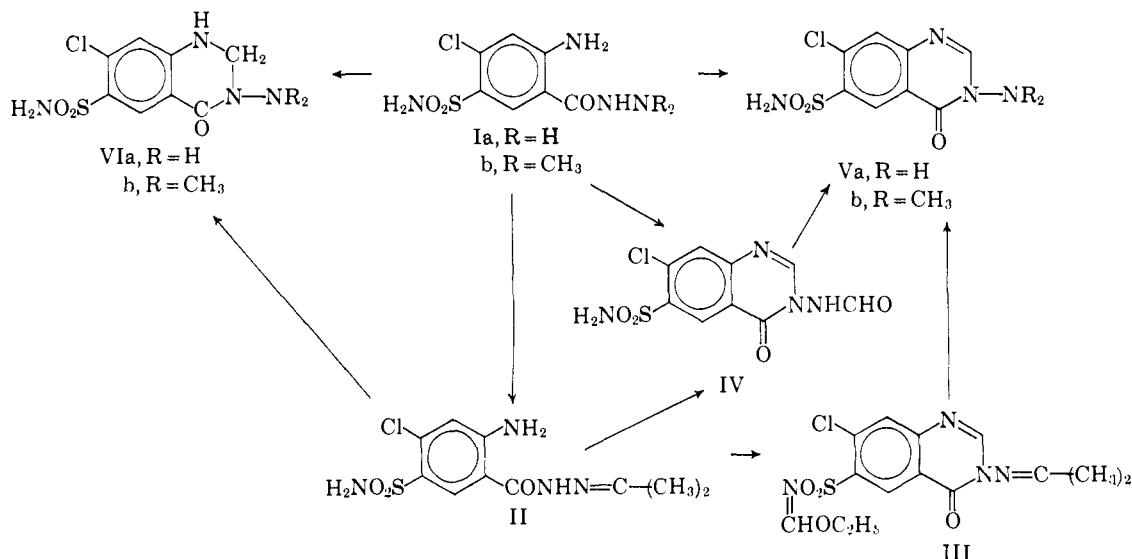
(5) E. Cohen, B. Klonberg, and J. R. Vaughn, Jr., *J. Am. Chem. Soc.*, **82**, 2731 (1960).

(6) All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Where analyses are indicated by symbols of the elements, analytical results obtained for these elements were within  $\pm 0.4\%$  of the theoretical values.

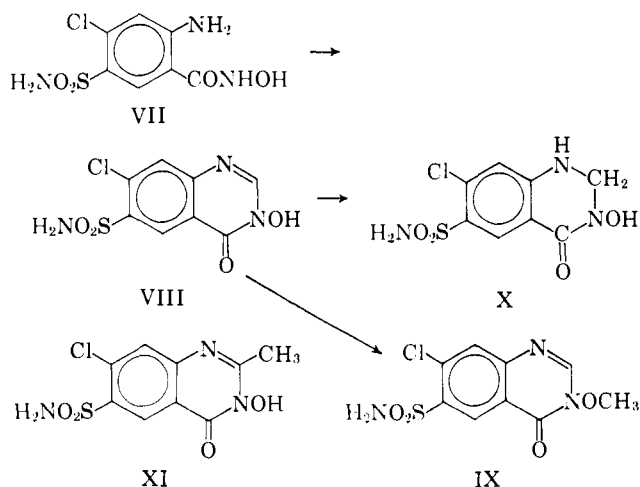
(1) M. L. Hoefle and H. A. DeWald, U. S. Patent 3,044,874 (1962).

(2) E. C. Taylor, O. Vogel, and P. K. Loeffler, *J. Am. Chem. Soc.*, **81**, 2479 (1959).

SCHEME I



SCHEME II



was concentrated under reduced pressure. H<sub>2</sub>O (150 ml) was added to the residue and the product was collected by filtration and dried in a vacuum oven at 60°; yield 51 g, mp 197–199°. Two recrystallizations from aqueous EtOH (1:1) yielded the analytical sample, mp 212–213°. *Anal.* (C<sub>9</sub>H<sub>8</sub>ClN<sub>3</sub>O<sub>4</sub>S) C, H.

**4-Chloro-5-sulfamoylanthranilic Acid Hydrazide (Ia).**—A solution of 10.0 g of 4-chloro-5-sulfamoylanthranilic acid cyanomethyl ester in 25 ml of 85% hydrazine hydrate was allowed to stand at room temperature for 6 hr. The reaction mixture was then diluted with 40 ml of aqueous AcOH (25%). The solid was removed by filtration and recrystallized from aqueous EtOH (1:1); yield 8.5 g, mp 252–254°. *Anal.* (C<sub>7</sub>H<sub>8</sub>ClN<sub>4</sub>O<sub>3</sub>S) C, H, N.

This product (8.5 g) and 50 ml of Me<sub>2</sub>CO were heated at reflux for 3 hr. The resulting product, 4-chloro-5-sulfamoylanthranilic acid isopropylidenehydrazide (II), was removed by filtration and recrystallized from aqueous EtOH (1:1); yield 8.5 g, mp 242–244°. *Anal.* (C<sub>10</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>3</sub>S) C, H.

**4-Chloro-5-sulfamoylanthranilic Acid 2,2-Dimethylhydrazide (Ib).**—To a solution of 25.0 g of 4-chloro-5-sulfamoylanthranilic acid in 100 ml of DMF was added 6.0 g of N,N-dimethylhydrazine followed by 20.4 g of N,N'-dicyclohexylcarbodiimide. The reaction mixture was stirred at room temperature for 24 hr while a precipitate slowly separated. This solid (N,N'-dicyclohexylurea) was collected by filtration and the filtrate was concentrated under reduced pressure. The gummy residue was extracted with 100 ml of 2 N HCl. The aqueous layer was removed by decantation and neutralized with NH<sub>4</sub>OH yielding 6.1 g of product, mp 239–240°. The analytical sample was prepared by recrystallization from EtOH; mp 250–251°. *Anal.* (C<sub>9</sub>H<sub>13</sub>N<sub>4</sub>O<sub>3</sub>S) C, H, N.

#### 2-Amino-4-chloro-5-sulfamoylbenzohydroxamic Acid (VII).

—To a chilled solution of 8.0 g of NaOH in 50 ml of H<sub>2</sub>O was added 7.0 g of HONH<sub>3</sub>+Cl<sup>-</sup>. A solution of 9.5 g of cyanomethyl 4-chloro-5-sulfamoylanthranilate in 75 ml of MeOH was added and the reaction mixture was allowed to stand at room temperature for 3 days. The MeOH was removed under reduced pressure, the aqueous solution was charcoaled and filtered, and the filtrate was made slightly acidic (pH 6) by the careful addition of concentrated HCl. BaCl<sub>2</sub>·2H<sub>2</sub>O (4.0 g) was added and the mixture was warmed gently on the steam bath until a complete solution was obtained. Concentrated NH<sub>4</sub>OH was added dropwise until the solution tested slightly basic (pH 8) and, on cooling, a precipitate was obtained. This was collected by filtration and after drying weighed 9.3 g, mp 270–280°. The barium salt (3.0 g) was added to 15 ml of H<sub>2</sub>O and 1 ml of concentrated HCl was added. Initially all was in solution, but upon cooling a solid was obtained; 1.5 g, mp 212–213°. Recrystallization from EtOH gave 1.1 g, mp 216°. *Anal.* (C<sub>7</sub>H<sub>8</sub>ClN<sub>3</sub>O<sub>4</sub>S) C, H.

**3-Substituted 3,4-Dihydro-4-oxo-6-quinazolines.** **Method A. N-(7-Chloro-3,4-dihydro-3-isopropylideneamino-4-oxo-6-quinazolinylsulfonamide)formimidic Acid Ethyl Ester (III).**—A solution of 4-chloro-5-sulfamoylanthranilic acid isopropylidenehydrazide (10.0 g), and 80 ml of ethyl orthoformate was heated and the EtOH formed during the course of the reaction was distilled through a short column. Heating was continued until the internal temperature reached 145°. This reaction temperature was maintained for 0.5 hr, and the mixture was filtered hot to remove a small amount of insoluble material. Upon cooling a solid crystallized out of the solution; 6.5 g, mp 175–180°. Recrystallization from MeCN raised the melting point to 185–186°. *Anal.* (C<sub>14</sub>H<sub>13</sub>ClN<sub>4</sub>O<sub>4</sub>S) C, H, N.

**Method B. N-(7-Chloro-4-oxo-6-sulfamoyl-3(4H)-quinazolinyl)formamide (IV).**—A solution of 4-chloro-5-sulfamoylanthranilic acid hydrazide (2.0 g) and formic acid (10 ml, 98%) was heated reflux for 2 hr. Then 30 ml of H<sub>2</sub>O was added and upon cooling the product precipitated; yield 1.8 g, mp 279–281°. The product was purified by recrystallization from aqueous EtOH (1:1); mp 284°. The formyl derivative (2.0 g) and 100 ml of 2 N HCl was heated on a steam bath until complete solution was obtained (approximately 15 min). The solution was cooled and neutralized with NH<sub>4</sub>OH yielding 1.4 g of 3-amino-7-chloro-3,4-dihydro-4-oxo-6-quinazolinylsulfonamide (Va), mp 260–265°. Purification by recrystallization from aqueous EtOH (1:1) raised the melting point to 273–274°.

4-Chloro-5-sulfamoylanthranilic acid 2,2-dimethylhydrazide (3.4 g) when treated with formic acid yielded 7-chloro-3-(dimethylamino)-3,4-dihydro-4-oxo-6-quinazolinylsulfonamide (Vb, 2.7 g, mp 221–222°). Similarly, 7-chloro-3,4-dihydro-3-hydroxy-4-oxo-6-quinazolinylsulfonamide (VIII, 1.75 g, mp 285°) was obtained by refluxing 4.0 g of the barium salt of 2-amino-4-chloro-5-sulfamoylbenzohydroxamic acid (VII) with formic acid.

**3-Substituted 1,2,3,4-Tetrahydro-4-oxo-6-quinazolines.** **Method C. 7-Chloro-3-dimethylamino-1,2,3,4-tetrahydro-4-oxo-**

TABLE I  
 3-SUBSTITUTED 7-CHLORO-4-OXO-6-QUINAZOLINESULFONAMIDES

Compd	R <sub>1</sub>	R <sub>2</sub>	Prepn method <sup>a</sup>	Yield, %	Mp, °C <sup>b</sup>	Formula <sup>c</sup>	Dose, <sup>d</sup> mg/kg	μequiv/kg/5 hr			
								Na <sup>e</sup>	K <sup>e</sup>	Cl <sup>e</sup>	HCO <sub>3</sub> <sup>e</sup>
Control								155	293	71	119
IV	H	NHCHO	B	90.8	284	C <sub>8</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>4</sub> S	2.5	716	814	651	416
Va	H	NH <sub>2</sub>	B	61.2	273-274	C <sub>8</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>3</sub> S	2.5	396	507	243	485
Vb	H	N(CH <sub>3</sub> ) <sub>2</sub>	B	76.8	220-221	C <sub>9</sub> H <sub>10</sub> ClN <sub>4</sub> O <sub>3</sub> S	2.5	842	510	1043	271
VIII	H	OH	B	53.1	288	C <sub>8</sub> H <sub>6</sub> ClN <sub>4</sub> O <sub>4</sub> S	2.5	1499	821	1843	268
IX	H	OCH <sub>3</sub>		72.4	260-262	C <sub>9</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>4</sub> S	2.5	1098	781	956	597
XI	CH <sub>3</sub>	OH		5.6	287-288	C <sub>9</sub> H <sub>8</sub> ClN <sub>4</sub> O <sub>4</sub> S	2.5	1133	593	754	701
VIa	H	NH <sub>2</sub>	C	33.4	262-264	C <sub>8</sub> H <sub>7</sub> ClN <sub>4</sub> O <sub>3</sub> S	2.5	780	625	949	259
VIb	H	N(CH <sub>3</sub> ) <sub>2</sub>	C	71.1	285-287	C <sub>9</sub> H <sub>10</sub> ClN <sub>4</sub> O <sub>3</sub> S	2.5	1677	729	2400	73
X	H	OH		20.3	246-247	C <sub>8</sub> H <sub>6</sub> ClN <sub>4</sub> O <sub>4</sub> S	2.5	2293	1031	2128	792
XII <sup>e</sup>	H	H					10	1407	1053	1849	52

<sup>a</sup> General method given in the Experimental Section. <sup>b</sup> All samples were recrystallized from ethanol or aqueous ethanol (1:1). <sup>c</sup> Satisfactory C, H, N analyses were obtained for the compounds listed. <sup>d</sup> Administered orally to dogs *via* gavage. <sup>e</sup> Compound XII is described by E. Cohen, *et al.*,<sup>5</sup> and is included in order to allow a comparison of diuretic activity.

**6-quinazolinesulfonamide (Vib).**—4-Chloro-5-sulfamoylanthranilic acid 2,2-dimethylhydrazide (6.5 g) and 1.76 g of aqueous H<sub>2</sub>CO (37%) were added to a solution of 30 ml of H<sub>2</sub>O, 5.0 ml of EtOH, and 2 drops of concentrated HCl. The solution was stirred at reflux for 5 hr. After cooling the product was removed by filtration and purified by recrystallization from EtOH; yield 4.8 g, mp 283-285°. The analytical sample was prepared by an additional recrystallization from EtOH, mp 285-287°.

**7-Chloro-1,2,3,4-tetrahydro-3-hydroxy-4-oxo-6-quinazoline-sulfonamide (X).**—Anhydrous AlCl<sub>3</sub> (1.03 g) was added to 250 ml of diglyme dried over CaH<sub>2</sub>. The solution was stirred while 2.2 g of 7-chloro-3,4-dihydro-3-hydroxy-4-oxo-6-quinazoline-sulfonamide was added, and it was then warmed gently on a steam bath until the reaction temperature was 60°. Warming was discontinued and a solution of 1.4 g of NaBH<sub>4</sub> in 70 ml of diglyme was added dropwise. The reaction mixture was heated at 75° for 1 hr and then at 85° for an additional 15 min. The resulting solution was cooled and 40 ml of H<sub>2</sub>O was added dropwise. It was acidified by adding dilute HCl (2 ml of concentrated acid in 10 ml of H<sub>2</sub>O) and concentrated to dryness on a rotary evaporator. The residue was triturated with 20 ml of cold H<sub>2</sub>O, and the product was removed by filtration; yield 1.7 g, mp 218-229°. This was purified by recrystallization from EtOH (95%) and yielded 0.45 g, mp 238°. The analytical sample was prepared by recrystallizing from aqueous Me<sub>2</sub>CO (1:1); mp 246-247°.

**7-Chloro-3,4-dihydro-3-methoxy-6-quinazolinesulfonamide (IX).**—7-Chloro-3,4-dihydro-3-hydroxy-4-oxo-6-quinazoline-sulfonamide (1.38 g) was dissolved in 5 ml of H<sub>2</sub>O containing 0.84 g of NaHCO<sub>3</sub>. This solution was then added to 0.63 g of Me<sub>2</sub>SO<sub>4</sub> and the reaction mixture was warmed to 60° by heating on a

steam bath. An additional 0.42 g of NaHCO<sub>3</sub> was added with stirring and the solid which had precipitated during the course of the reaction was collected by filtration and dried; yield 1.05 g, mp 249-252°. Two recrystallizations from a mixture of H<sub>2</sub>O-EtOH (1:9) yielded 0.55 g, mp 260-262°.

**7-Chloro-3,4-dihydro-3-hydroxy-2-methyl-4-oxo-6-quinazoline-sulfonamide (XI).**—A solution of 10.0 g of 4-chloro-5-sulfamoylanthranilic acid in 30 ml of Ac<sub>2</sub>O was heated at reflux for 2 hr. Concentration on a rotary evaporator under reduced pressure yielded 9.5 g of a viscous oil which could not be induced to crystallize. Hence, it was added directly to an aqueous solution of HONH<sub>2</sub> (prepared by adding 12.0 g of NaOH to a chilled solution of 21.0 g of HONH<sub>3</sub><sup>+</sup>·Cl<sup>-</sup> in 100 ml of H<sub>2</sub>O). Small portions of 10% NaOH (total = 40 ml) were added over a period of 0.5 hr to keep reaction mixture at a pH > 8. The solution was then heated on the steam bath for 10 min, cooled, and made acidic with concentrated HCl. The precipitate (2.1 g) was removed by filtration and identified as starting material. The filtrate was allowed to stand overnight in the refrigerator and a second crop of crystals was obtained that gave a red-orange color with ferric chloride solution. Two recrystallizations from aqueous EtOH (1:1) yielded 0.65 g of product melting at 287-288°.

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