TABLE III
Ascaris suum IN SWINE[a]

No.	Dose, % in feed	Liver lesions	No. of larvae in lungs	Lung pathol
III	0.02	>500	0–600	0–0
	0.04	140–160	0–600	0–0
XVI	0.01	54–125	0–400	0–0
XVIII	0.01	9–86	400–1600	0–1
Unmedicated controls		>500	10,000–15,000	3–4

[a] The test compounds were administered at the stated dosage level in feed for a period of 10 days to two pigs in concrete-floored pens. An infection of 10,000 embryonated *Ascaris suum* eggs was administered 3 days after the start of the inclusion of the test compound in the feed. The animals were sacrificed after 10 days and examined for liver lesions and lung pathology.

Experimental Section[14]

3,3′-Diethyl-6,6′-dimethylthiadicarbocyanine Iodide (VI).—Triethylamine (7.3 ml) was added to a refluxing solution of 2,6-dimethyl-3-ethylbenzothiazolium iodide[15] (16.0 g, 0.05 mole) and 1-methyl-1,2-dihydro-2-iminopyrimidine hydriodide[4] (5.9 g, 0.025 mole) in ethanol (150 ml). The resulting deep blue mixture was refluxed for 30 min, cooled, and filtered, giving VI, mp 259–260°, yield 9.5 g (70%).

The other symmetrical thiadicarbocyanines listed in Table I were prepared in the same way.

2-(4-Dimethylamino-1,3-butadienyl)-3-methyl-6-ethoxybenzothiazolium Iodide (XIX).—A mixture of 2,3-dimethyl-6-ethoxybenzothiazolium iodide[16] (12.0 g, 0.035 mole) and N,N′-1-propen-1-yl-3-ylidenedianiline hydrochloride (9.1 g, 0.035 mole) in acetic anhydride (100 ml) was refluxed for 1 hr. The mixture was cooled and filtered, giving 2-(4-acetanilido-1,3-butadienyl)-3-methyl-6-ethoxybenzothiazolium iodide, mp 230–232°, yield 15.0 g. The acetanilido derivative (14 g) was added to a solution of dimethylamine (10 g) in ethanol (50 ml), and the mixture was refluxed for 30 min. The product, which separated out on cooling, was filtered and recrystallized from methanol to a constant melting point of 231° dec, yield 9.6 g (66%).

The other hemithiacyanines listed in Table II were made in the same way.

2,3-Dimethyl-6-nitrobenzothiazolium Iodide.—2-Methyl-6-nitrobenzothiazole[17] (25 g, 0.13 mole) was heated with methyl iodide (23 g, 0.16 mole) in a pressure bottle at 100° for 24 hr. The solid product was triturated in ether, giving 1.4 g (99%), mp 240° dec after recrystallization from nitromethane.

Anal. Calcd for $C_9H_9IN_2O_2S$: C, 32.15; H, 2.70; I, 37.76; N, 8.33; S, 9.54. Found: C, 32.25; H, 2.96; I, 38.10; N, 8.26; S, 9.53.

Acknowledgment.—The authors are indebted to Dr. A. O. Geiszler for invaluable help in the coordination of the research program.

(14) Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are corrected. Elementary analyses were performed by the Microanalytical Laboratory, Abbott Laboratories, North Chicago, Ill.

(15) H. C. Barany and M. Pianka, *J. Chem. Soc.*, 2217 (1953).

(16) M. Q. Doja and J. C. Banerjee, *J. Indian Chem. Soc.*, **28**, 7 (1951).

(17) Y. Mizuno and K. Adachi, *J. Pharm. Soc. Japan*, **72**, 739 (1952); *Chem. Abstr.*, **48**, 2689 (1954).

Pyrazine Diuretics. IV. N-Amidino-3-amino-6-substituted Pyrazinecarboxamides

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The synthesis of a series of N-amidino-3-amino-6-substituted pyrazinecarboxamides is described. Since more direct synthetic routes were unsuccessful, the intermediate 3-amino-6-substituted pyrazinecarboxylic acids were synthesized by nucleophilic displacement of the chlorine from 6-chloro-4(3H)-pteridinones or their 3-methyl derivatives, followed by alkaline hydrolysis. These were cyclized to the 2-methyl-6-substituted 4H-pyrazino[2,3-*d*][1,3]oxazin-4-ones, which upon reaction with a guanidine followed by hydrolysis, afforded the desired compounds. When the N-amidino-3-amino-6-substituted pyrazinecarboxamides were assayed for saluretic and diuretic activity in normal rats, the 6-methylmercapto and the 6-benzylmercapto derivatives proved to be the most potent, while in the corresponding 3-acetamido series, the outstanding members were the 6-methylmercapto and the 6-methoxy derivatives.

The observation that the diuretic activity of N-amidino-3-aminopyrazinecarboxamide is markedly increased by the introduction of a 6-halo[1] or 6-methyl[2] substituent prompted the extension of the series to include a variety of 6-substituted derivatives (VIII and IX).

Chemistry.—The synthetic route for the compounds of this series is summarized by Scheme I. Since this route affords the intermediate 3-amino-6-substituted pyrazinecarboxylic acids (V), it was found most convenient to prepare the N-amidino-3-amino-6-substituted pyrazinecarboxamides (IX) by the previously described method[1] involving the reaction of a "cyclic iminoanhydride," 2-methyl-6-substituted 4H-pyrazino[2,3-*d*][1,3]-oxazin-4-one (VII), with guanidine followed by hydrolysis of the 3-acetamido intermediate (VIII).

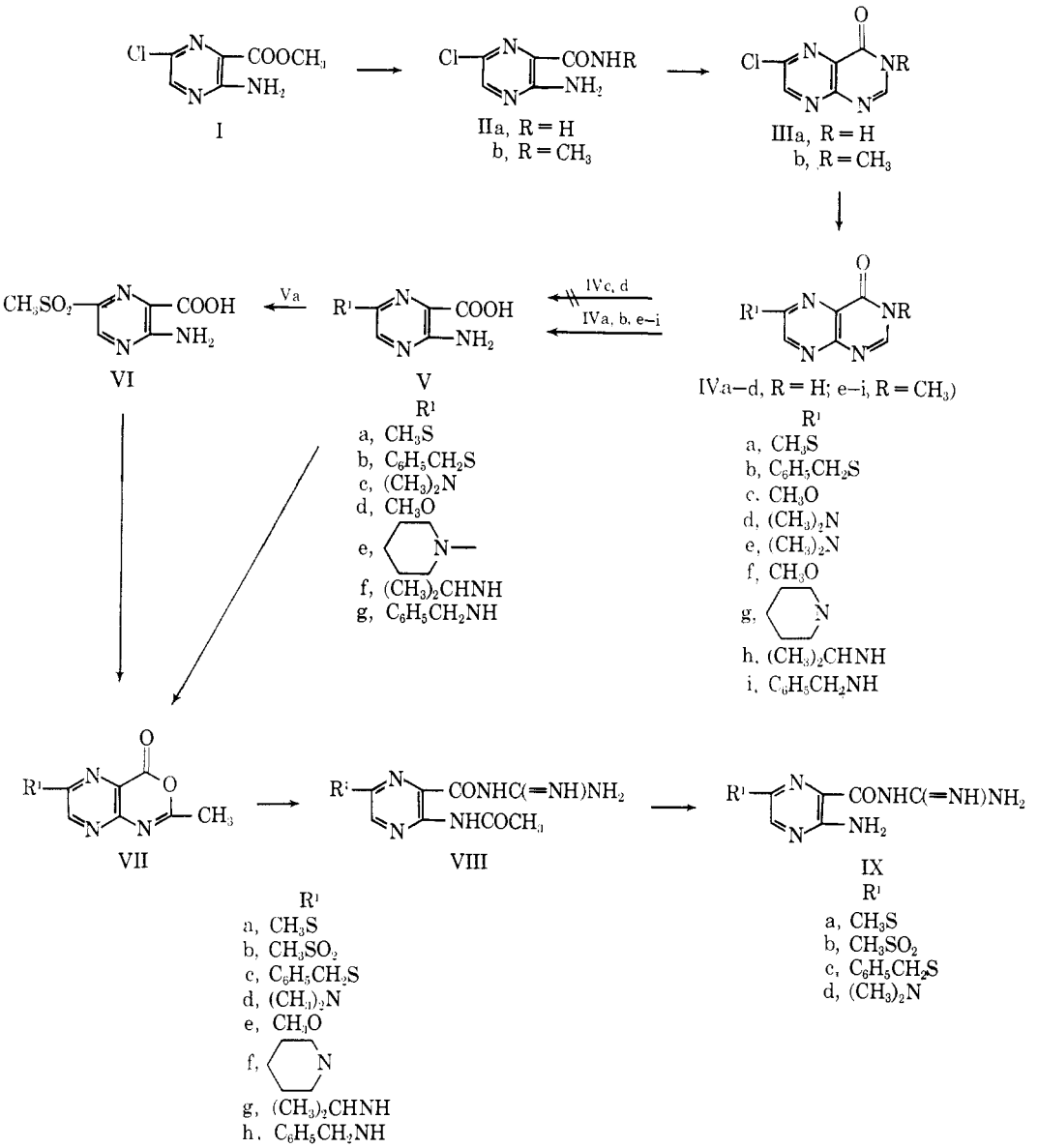
In this way, the reaction was carried out with "iminoanhydrides" (VII) bearing eight different 6-substituents (VIIa–h). The N-amidino-3-acetamido-6-substituted pyrazinecarboxamides (VIII) were readily isolated, and, except in two instances (VIIIb and c), they were characterized. Representative members of the series were hydrolyzed to the corresponding N-amidino-3-amino-6-substituted pyrazinecarboxamides (IX).

Initially, attempts were made to prepare the intermediate 3-amino-6-substituted pyrazinecarboxylic acids

(1) Paper I of this series: J. B. Bicking, J. W. Mason, O. W. Woltersdorf, Jr., J. H. Jones, S. F. Kwong, C. M. Robb, and E. J. Cragoe, Jr., *J. Med. Chem.*, **8**, 638 (1965).

(2) Paper III of this series: J. B. Bicking, C. M. Robb, S. F. Kwong, and E. J. Cragoe, Jr., *ibid.*, **10**, 598 (1967).

SCHEME I



(V) *via* the reaction of methyl 3-amino-6-chloropyrazinecarboxylate (I) with various nucleophilic reagents. However, even under the most rigorous conditions amines, sodium alkoxides, and sodium mercaptides failed to react.

In a search for alternate routes to these intermediates (V) it was noted[3] that the halogen atom of 6-halopteridines is readily susceptible to nucleophilic displacement. 6-Chloro-4(3H)-pteridinone (IIIa) was prepared by heating 3-amino-6-chloropyrazinecarboxamide (IIa) with a mixture of acetic anhydride and ethyl orthoformate according to a well-known method.[4] The N-methylamide (IIb) afforded the homologous 3-methyl-6-chloro-4(3H)-pteridinone (IIIb). The reaction of these pteridinones with a variety of sodium alkoxides, sodium mercaptides, and amines gave the desired 6-substituted pteridinone (IVa–i).

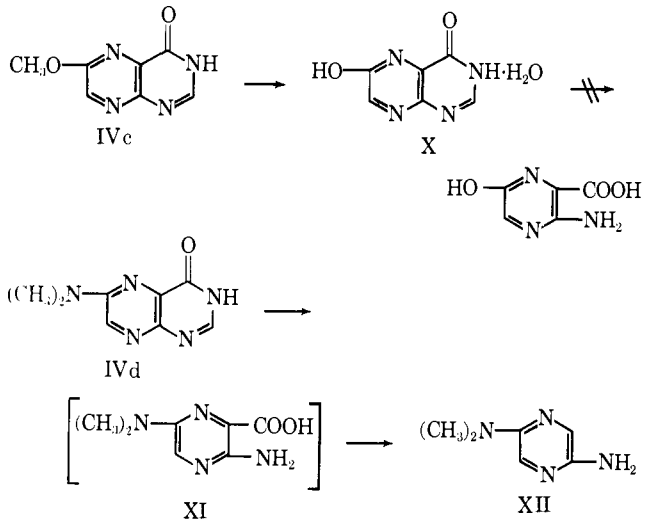
Since the hydrolytic cleavage of 4(3H)-pteridinones had been reported[5] it was anticipated that the reaction could be applied to our 6-substituted derivatives (IVa–d). Indeed, the 6-methylmercapto (IVa) and 6-benzylmercapto (IVb) compounds yielded the corresponding 3-amino-6-substituted pyrazinecarboxylic acids (Va and b). However, with 6-methoxy-4(3H)-pteridinone (IVc) the product was 6-hydroxy-4(3H)-pteridinone[6] (X). Attempts to effect further hydrolysis using more vigorous conditions were unsuccessful (Scheme II).

Attempted hydrolytic cleavage of 6-dimethylamino-4(3H)-pteridinone (IVd) did not give the desired 3-amino-6-dimethylaminopyrazinecarboxylic acid (XI) but rather the decarboxylated derivative XII (Scheme II).

When 3-methyl-6-substituted 4(3H)-pteridinones (IVe–i) were used, much more satisfactory results were achieved since hydrolytic cleavage occurred under milder conditions. Although this observation was anticipated from the studies of Albert, *et al.*,[7] the

(3) A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.*, 1621 (1952).
(4) E. C. Taylor, Jr., *J. Am. Chem. Soc.*, **74**, 1651 (1952).
(5) A. Albert, *Quart. Rev.* (London), **6**, 211 (1952).
(6) A. Albert and D. J. Brown, *J. Chem. Soc.*, 74 (1953).
(7) A. Albert, D. J. Brown, and H. C. S. Wood, *ibid.*, 2006 (1956).

SCHEME II



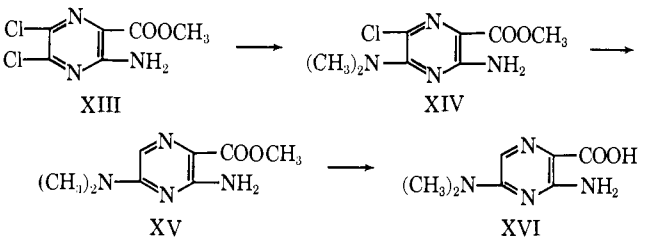
marked improvement in the method is noteworthy. Thus, 3-amino-6-methoxypyrazinecarboxylic acid and various 6-substituted amino analogs (Vc–g) were prepared in good yields by this procedure.

3-Amino-6-mesylpyrazinecarboxylic acid (VI) was prepared by the alkaline permanganate oxidation of the corresponding 6-methylmercapto compound (Va).

One of the most common routes for the synthesis of N-amidinopyrazinecarboxamides is by the interaction of the alkyl pyrazinecarboxylates with guanidine. Therefore, attempts were made to convert the various 3-amino-6-substituted pyrazinecarboxylic acids (V) to the corresponding esters by several methods. However, under acidic reaction conditions extensive decarboxylation occurred. In fact, the tendency for the 3-amino-6-substituted pyrazinecarboxylic acids (V) to decarboxylate made it advisable to isolate them from the hydrolytic cleavage reaction in the form of the sodium salts.

The synthesis of 3-amino-6-dimethylaminopyrazinecarboxylic acid (Vc) was of interest since it contributed to the structure proof of methyl 3-amino-5-dimethylaminopyrazinoate (XV) which we had reported previously.[8] Compound XV, which had been prepared as shown in Scheme III, was hydrolyzed to the corre-

SCHEME III

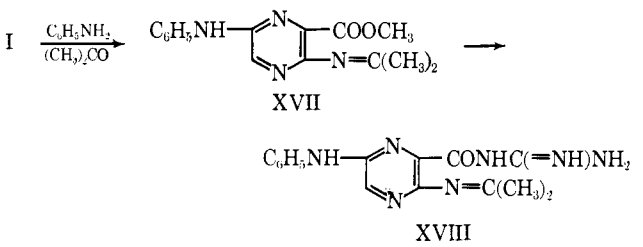


sponding acid (XVI) and shown to be different from but isomeric with Vc.

The 2-methyl-6-substituted 4H-pyrazino[2,3-*d*][1,3]-oxazin-4-ones (VIIa–h) were prepared by the reaction of the appropriate 3-amino-6-substituted pyrazinecarboxylic acids (V or VI) with acetic anhydride according to the method described earlier.[1] These "iminoanhydrides" (VII) are especially useful when the esters are not accessible or where the ester is not adequately reactive with a particular guanidine. The "iminoanhydrides"[11] also provide the 3-acetamido derivatives (VIII) which are not accessible by other routes.

Although direct displacement of the halogen atom of I by nucleophilic reagents is not generally successful, it was found that heating I with aniline and HCl in acetone gave methyl 3-isopropylideneamino-6-anilinopyrazinoate (XVII) which upon reaction with guanidine afforded the corresponding acylguanidine (XVIII) as shown in Scheme IV. If aniline was omitted or if

SCHEME IV



acetone was replaced by ethanol, no reaction occurred. The reaction also failed when *p*-anisidine or *p*-chloroaniline were substituted for aniline.

Structure–Activity Relationships.—Each of the N-amidino-3-amino- (and acetamido-) 6-substituted pyrazinecarboxamides (VIII and IX) which were prepared in this study were assayed for their deoxycorticosterone acetate (DOCA) inhibitory activity using the adrenalectomized rat according to the method described earlier.[1,8,9] The compounds were administered by the subcutaneous route. A scoring system similar to that described previously[8] was used and the data are recorded in Table I. In this test each of the ten compounds exhibited weak activity, except for the 3-acetamido-6-benzylamino compound (VIIIh) which was inactive at a dose of 800 μg.

These ten compounds also were tested intraperitoneally in normal rats[10] using a previously described method.[11] The relative potency of the compounds was based upon an assay (at doses of 5 and 50 mg/kg) in which the increase of electrolyte (Na^+ and Cl^-) and urine volume over control values were considered. Under these conditions hydrochlorothiazide, chlorothiazide, and controls are scored +3, +2, and 0, respectively. Compounds with activities between chlorothiazide and controls are scored +1 or ±.

Using the normal rat assay, a greater spread in activity is noted for the compounds under consideration than was observed with the DOCA inhibition assay. In the 3-acetamido series (VIII) relatively good activity is seen with the 6-methylthio (VIIIa) and 6-methoxy (VIIIe) compounds while the other members exhibit little or no activity. Similar results are observed in the 3-amino series where only the 6-methylthio (IXa) and 6-benzylthio (IXc) are active. From the available data it would appear that the N-amidino-3-amino- (and acetamido-) 6-substituted pyrazines reported

(8) Paper 11 in this series: E. J. Cragoe, Jr., O. W. Woltersdorf, Jr., J. B. Bicking, S. F. Kwong, and J. H. Jones, *J. Med. Chem.*, **10**, 66 (1967).

(9) M. S. Glitzer, S. L. Steelman, and their associates are responsible for these assays.

(10) Dr. J. E. Baer and his associates carried out these assays and supplied these data.

(11) E. J. Cragoe, Jr., O. W. Woltersdorf, Jr., J. E. Baer, and J. M. Sprague, *J. Med. Chem.*, **5**, 896 (1962).

TABLE I

No.	R	R₁	Method of syn[a]	Recrystn solvent[b]	% yield	Mp, °C	Formula	Carbon, % Calcd	Carbon, % Found	Hydrogen, % Calcd	Hydrogen, % Found	Nitrogen, % Calcd	Nitrogen, % Found	DOCA inhib score[g]	Normal rat score[g]
3-Amino-6-chloropyrazinecarboxamides															
IIa	H		1	W	88	231–232	$C_5H_5ClN_4O$	34.80	35.28	2.92	3.38	32.47	32.55		
IIb	CH_3		1	E	87	152–154	$C_6H_7ClN_4O$	38.62	38.62	3.78	3.82	30.03	29.71		
6-Chloro-4(3H)-pteridinones															
IIIa	H		2	I–W	57	268–270 dec	$C_6H_3ClN_4O$	39.27	39.61	1.65	1.87	30.69	31.03		
IIIb	CH_3		2	M	82	217–219	$C_7H_5ClN_4O$	42.76	42.85	2.65	2.79	28.50	28.15		
6-Substituted 4(3H)-Pteridinones															
IVa	H	CH_3S	3A	I–W	36	289–291	$C_7H_6N_4OS$	43.29	43.86	3.12	3.34				
IVb	H	$C_6H_5CH_2S$	3A	I–W	68	231–233	$C_{13}H_{10}N_4OS$	57.76	57.79	3.73	3.95	20.73	20.59		
IVc	H	CH_3O	3B	I–W	54	283–286 dec	$C_7H_6N_4O_2$	47.19	47.28	3.39	3.76	31.45	31.77		
IVd	H	$(CH_3)_2N$	3C	I–W	75	294–296	$C_8H_9N_5O$	50.25	50.56	4.74	4.91	36.63	36.72		
IVe	CH_3	$(CH_3)_2N$	3C	M	72	256–258	$C_9H_{11}N_5O$	52.67	52.99	5.40	5.39	34.13	34.19		
IVf	CH_3	CH_3O	3B	E	98	232–234	$C_8H_8N_4O_2$	50.00	50.53	4.20	4.47	29.16	29.04		
IVg	CH_3	$C_5H_{10}N$[f]	3C	B	56	207–209	$C_{12}H_{16}N_5O$	58.76	59.16	6.16	5.91	28.55	28.80		
IVh	CH_3	$(CH_3)_2CHNH$	3C			[c]									
IVi	CH_3	$C_6H_5CH_2NH$	3C	E	60	212–214	$C_{14}H_{13}N_5O$	62.91	62.90	4.90	5.09	26.20	25.95		
3-Amino-6-substituted Pyrazinecarboxylic Acids															
Va		CH_3S	4A	T	30	182–184 dec	$C_6H_7N_3O_2S$	38.91	39.58	3.81	3.98				
Vb		$C_6H_5CH_2S$	4A	T	35	138–139	$C_{12}H_{11}N_3O_2S$	55.16	54.75	4.24	4.10	16.08	15.96		
Vc		$(CH_3)_2N$	4B	M	79	164.5–165.5 dec	$C_7H_{10}N_4O_2$	46.15	46.32	5.53	5.71	30.76	30.68		
Vd		CH_3O	4B			[d]									
Ve		$C_5H_{10}N$[f]	4B			[d]									
Vf		$(CH_3)_2CHNH$	4B			[d]									
Vg		$C_6H_5CH_2NH$	4B	W	98	130–132 dec	$C_{14}H_{12}N_3O_2$	59.01	58.94	4.95	5.13	22.94	22.86		
VI		CH_3SO_2	4C	I	46	239–242 dec	$C_6H_7N_3O_4S$	33.18	33.81	3.25	3.35	19.35	18.88		
2-Methyl-6-substituted 4H-Pyrazino[2,3-*d*][1,3]oxazin-4-ones															
VIIa		CH_3S	5	B	94	189–191	$C_8H_7N_3O_2S$	45.92	46.11	3.37	3.42	20.08	20.04		
VIIb		CH_3SO_2	5	A	58	214–216	$C_8H_7N_3O_4S$	39.83	40.23	2.93	2.92	17.42	17.27		
VIIc		$C_6H_5CH_2S$	5	B	76	116–118	$C_{14}H_{11}N_3O_2S$	58.93	58.99	3.89	3.93	14.73	14.68		
VIId		$(CH_3)_2N$	5	B	66	210 dec	$C_9H_{10}N_4O_2$	52.42	52.89	4.89	5.12	27.17	27.04		
VIIe		CH_3O	5	B	52	190–192	$C_8H_7N_3O_3$	49.74	49.79	3.65	3.52	21.75	21.81		
VIIf		$C_5H_{10}N$[f]	5	B	45	172–174	$C_{13}H_{14}N_4O_2$	58.52	58.49	5.73	5.74	22.75	22.86		
VIIg		$(CH_3)_2CHNH$	5	B	38	212–214	$C_{13}H_{12}N_4O_2$	54.54	54.61	5.49	5.42	25.44	25.11		
VIIh		$C_6H_5CH_2NH$	5	B	30	168–170	$C_{14}H_{12}N_4O_2$	62.68	62.49	4.51	4.69	20.88	20.80		
N-Amidino-3-acetamido-6-substituted Pyrazinecarboxamides															
VIIIa		CH_3S	6	P	68	220–222 dec	$C_9H_{12}N_6O_2S$	40.29	39.90	4.51	4.39	31.33	31.39	±	2
VIIIb		CH_3SO_2	6			[e]									
VIIIc		$C_6H_5CH_2S$	6			[e]									
VIIId		$(CH_3)_2N$	6	W	44	236 dec	$C_{10}H_{16}N_7O_2 \cdot HNO_3$	36.59	36.53	4.91	5.02	34.13	34.27	±	±
VIIIe		CH_3O	6	W	33	225 dec	$C_9H_{12}N_6O_3 \cdot HNO_3$	34.29	34.68	4.16	4.30	31.10	31.10	±	2
VIIIf		$C_5H_{10}N$[f]	6	W	75	228 dec	$C_{13}H_{19}N_7O_2 \cdot HNO_3$	42.39	42.75	5.47	5.32	30.42	30.79	±	0
VIIIg		$(CH_3)_2CHNH$	6	W	44	203–205 dec	$C_{12}H_{17}N_7O_2 \cdot HNO_3$	38.60	38.79	5.30	5.35	32.73	32.60	±	0
VIIIh		$C_6H_5CH_2NH$	6	W	28	225–228 dec	$C_{15}H_{17}N_7O_2 \cdot HNO_3$	46.15	46.44	4.65	4.65	28.71	28.40	0	±
N-Amidino-3-amino-6-substituted Pyrazinecarboxamides															
IXa		CH_3S	7	I–W	65	202–203 dec	$C_7H_{10}N_6OS$	37.16	37.43	4.45	4.51	37.15	37.06	±	2
IXb		CH_3SO_2	7	I–W	20	222–224 dec	$C_7H_{10}N_6O_2S$	32.55	32.82	3.90	3.70	32.54	32.19	±	0
IXc		$C_6H_5CH_2S$	7	I–W	92	171–173 dec	$C_{13}H_{14}N_6OS$	51.64	51.85	4.67	4.82	27.80	27.62	±	2
IXd		$(CH_3)_2N$	7	P	73	195–197 dec	$C_8H_{13}N_7O$	43.04	42.80	5.87	6.00	43.92	43.94	±	±

[a] The number and letter corresponds to those in the Experimental Section. [b] A, acetone; B, benzene; E, ethanol; I, isopropyl alcohol; M, methanol; P, dissolved in dilute aqueous hydrochloric acid and precipitated with dilute aqueous sodium hydroxide; T, ethyl acetate; W, water. [c] The compound failed to crystallize; therefore, the solvent was removed from the reaction mixture by reduced pressure distillation and the residue used in the next reaction. [d] The sodium salt of the pyrazinecarboxylic acid which separated upon cooling the reaction mixture was used directly in the next reaction. [e] This compound was isolated but not purified and characterized before use in the next reaction. [f] Piperidino. [g] The DOCA inhibition score is the dose producing 50% reversal of the DOCA Na/K effect: +2 = 50–100 μg/rat, +1 = 101–800, ± = >800, 0 = no activity at 800 μg. Although no statistically significant activity was noted at the last dose, the possibility of activity at higher doses exists. Also, it will be noted that compounds inactive in this assay are active in the normal rat assay.

here are more kaliuretic than those described previously.[1,2,8]

Compound XVIII exhibited weak activity (±)[12] in the DOCA inhibition assay but not in the normal rat test.

Experimental Section[13]

Pertinent details regarding the synthesis and physical properties of each new compound are presented. Where one method is used to prepare more than one compound in a series, an exemplary procedure is described and a summary of the details regarding other members of the series is recorded in Table I.

3-Amino-6-halopyrazinecarboxamides (II). N-Methyl-3-amino-6-chloropyrazinecarboxamide (IIb).—A suspension of I[1] (20 g, 0.107 mole) in 40% aqueous methylamine (200 ml) was stirred at room temperature for 20 hr. The solid product was removed by filtration, washed with water, and dried. The yield was 17.5 g (87%), mp 151–154°. After recrystallization from ethanol IIb melted at 152–154°.

6-Chloro-4(3H)-pteridinones (III). 6-Chloro-4(3H)-pteridinone (IIIa).—A mixture of IIa (33 g, 0.19 mole), acetic anhydride (200 ml), and triethyl orthoformate (200 ml) was refluxed for 1.5 hr and then cooled. The product that separated was recovered by filtration and recrystallized from aqueous isopropyl alcohol. The yield was 20 g (57%), mp 268–270° dec.

(12) See Table I for an explanation of the score.

(13) All melting points were taken using open capillaries and are corrected values. The analytical data has been supplied by K. B. Streeter, Y. C. Lee, and their staff.

6-Substituted 4(3H)-Pteridinones (IV). A. 6-Methylmercapto-4(3H)-pteridinone (IVa).—Methyl mercaptan (4.8 g, 0.1 mole) was dissolved in 10% aqueous NaOH (60 ml) and added to a stirring solution of IIIa (9.1 g, 0.05 mole) in 4% aqueous NaOH (100 ml). The mixture was stirred and heated on a steam bath for 20 min and then chilled. The sodium salt which precipitated was separated by filtration and dissolved in hot water. Acidification of the solution (HCl) gave IVa which was separated and recrystallized from aqueous isopropyl alcohol; yield 3.5 g (36%), mp 289–291°.

B. 6-Methoxy-4(3H)-pteridinone (IVc).—Sodium (1.2 g, 0.052 g-atom) was dissolved in methanol (100 ml), IIIa (3.6 g, 0.02 mole) was added, and the solution was refluxed for 4 hr. After cooling, water (150 ml) was added and the solution was acidified (HCl). The solid that separated was removed by filtration and recrystallized from aqueous isopropyl alcohol; the yield was 1.9 g (54%), mp 283–286° dec.

C. 3-Methyl-6-dimethylamino-4(3H)-pteridinone (IVe).—A solution of 25% aqueous dimethylamine (5 ml) in 2-methoxyethanol (40 ml) was stirred and treated with IIIb (4.0 g, 0.02 mole). The solution was heated on a steam bath for 2.5 hr and then chilled. The solid that precipitated was separated by filtration, washed with cold methanol, and dried; the yield was 3.0 g (72%), mp 251–256°. After recrystallization from methanol, mp 256–258°.

With other members of the series, if the product failed to separate from the reaction mixture, the addition of water caused it to precipitate.

3-Amino-6-substituted Pyrazinecarboxylic Acids. A. 3-Amino-6-methylmercaptopyrazinecarboxylic Acid (Va).—A solution of IVa (25.5 g, 0.13 mole) in 5% NaOH (250 ml) was stirred and heated on a steam bath for 13 hr. The sodium salt of the product which separated upon cooling the reaction mixture was removed by filtration and dissolved in hot water. Acidification gave Va which was recrystallized from ethyl acetate to give 7.1 g (30%), mp 182–184° dec.

B. 3-Amino-6-dimethylaminopyrazinecarboxylic Acid (Vc).—A suspension of IVe (1.0 g, 5 mmoles) in 10% aqueous NaOH (15 ml) was stirred and heated on a steam bath for 2.5 hr and the solid gradually dissolved. The solution was chilled and carefully neutralized with formic acid which precipitated Vc (700 mg, 79%), mp 161–165° dec. Recrystallization from methanol gave material melting at 164.5–165.5° dec.

C. 3-Amino-6-mesylpyrazinecarboxylic Acid (VI).—A stirred solution of Va (920 mg, 5 mmoles) in 2.5% aqueous NaOH (15 ml) was treated with a solution of $KMnO_4$ (1.05 g, 6.7 mmoles) in water (35 ml). After stirring 1 hr at ambient temperature, MnO_2 was removed by filtration and the filtrate was acidified (HCl). The precipitate was separated by filtration, dried, and recrystallized from isopropyl alcohol; yield 500 mg (46%), mp 239–242° dec.

2-Methyl-6-substituted 4H-Pyrazino[2,3-*d*][1,3]oxazin-4-ones (VII). 2-Methyl-6-dimethylamino-4H-pyrazino[2,3-*d*][1,3]-oxazin-4-one (VIId).—A solution of Vc (2.0 g, 11 mmoles) in acetic anhydride (25 ml) was heated for 2.5 hr on a steam bath and then cooled. The product which separated was removed by filtration, dried, and recrystallized from benzene; yield 1.5 g (66%), mp 212° dec.

When the reaction was carried out using the sodium pyrazinecarboxylate, it was advantageous to remove the sodium acetate that formed before isolating the product.

N-Amidino-3-acetamido-6-substituted Pyrazinecarboxamides (VIII). N-Amidino-3-acetamido-6-dimethylaminopyrazinecarboxamide (VIIId).—Sodium (500 mg, 0.0217 g-atom) was dissolved in methanol (30 ml), then guanidine hydrochloride (2.0 g, 11 mmoles) was added and the mixture refluxed for 30 min. After cooling, the mixture was stirred and treated with VIId (1 g, 4.8 mmoles) and stirring at ambient temperature was continued for 3 hr. The reaction mixture was poured into water (100 ml) and filtered, and the filtrate was acidified (AcOH). Compounds VIIIa–c separated at this point and were removed by filtration. Compounds VIIId, e, g, and h remained in solution at this point and were isolated as described for VIIId. Upon addition of dilute HNO_3 (1 ml), VIIId·NHO_3 separated. Recrystallization from water gave 700 mg (44%), mp 236° dec.

N-Amidino-3-amino-6-substituted Pyrazinecarboxamides (IX). N-Amidino-3-amino-6-dimethylaminopyrazinecarboxamide (IXd).—A solution of VIIId·HNO_3 (500 mg, 1.5 mmoles) in 10% HCl (10 ml) was heated on a steam bath for 15 min, then cooled and carefully neutralized with 5% NaOH. The product that separated was dissolved in 5% HCl and reprecipitated with 5% aqueous NaOH to give 250 mg of IXd, mp 195–197° dec.

6-Hydroxy-4(3H)-pteridinone Hydrate (X).—A solution of IVc (3 g, 17 mmoles) in 5% NaOH (30 ml) was heated on a steam bath for 18 hr and then cooled. Addition of 40% NaOH (10 ml) precipitated the sodium salt of X which was removed by filtration, dissolved in water, treated with decolorizing charcoal, and filtered. Acidification of the filtrate (HCl) gave 1.7 g (55%) of X, mp >300°.

Anal. Calcd for $C_6H_4O_2 \cdot H_2O$: C, 39.56; H, 3.32; N, 30.76. Found: C, 39.94; H, 3.24; N, 30.86.

The chemical properties and uv spectra of this material agree with that reported by Albert and Brown[6] who prepared X by another route.

2-Amino-5-dimethylaminopyrazine (XII).—A solution of IVd (1.9 g, 10 mmoles) in 5% NaOH (20 ml) was heated at 140° in an autoclave for 18 hr. After cooling, the reaction mixture was twice extracted ($CHCl_3$, 50-ml portions) and the combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated *in vacuo*. The residual material, 400 mg (29%), was recrystallized from cyclohexane to give XII, mp 84–86°.

Anal. Calcd for $C_6H_{10}N_4$: C, 52.15; H, 7.30. Found: C, 52.05; H, 6.95.

3-Amino-5-dimethylaminopyrazinecarboxylic Acid (XVI).—A suspension of XV[8] (300 mg, 1.5 mmoles) in 5% NaOH (20 ml) was stirred and heated on a steam bath for 30 min during which time the solid dissolved. The warm solution was carefully neutralized with dilute HCl. The precipitate (250 mg, 90%) was separated by filtration and recrystallized from aqueous isopropyl alcohol, mp 231–232°.

Anal. Calcd for $C_7H_{10}N_4O$: C, 46.15; H, 5.52; N, 30.76. Found: C, 46.50; H, 5.64; N, 31.13.

Methyl 3-Isopropylideneamino-6-anilinopyrazinecarboxylate (XVII).—A solution of I (18.8 g, 0.1 mole), aniline (15 g, 0.16 mole), and concentrated HCl (2.5 ml) in acetone (150 ml) was refluxed for 16 hr and then chilled. The crystalline product which separated was removed by filtration and recrystallized several times from aqueous isopropyl alcohol; yield 7.4 g (26%), mp 195.5–197.5°.

Anal. Calcd for $C_{15}H_{16}N_4O_2$: C, 63.36; H, 5.67; N, 19.71. Found: C, 63.45; H, 5.66; N, 19.81.

N-Amidino-3-isopropylideneamino-6-anilinopyrazinecarboxamide (XVIII).—Sodium (2.3 g, 0.1 g-atom) was dissolved in methanol (60 ml), guanidine hydrochloride (11.5 g, 0.12 mole) was added, and the mixture refluxed for 30 min. The solution was cooled and filtered, and the filtrate was concentrated to a syrup *in vacuo*. Benzene (20 ml) was added and the solution was concentrated to a syrup *in vacuo*. After adding XVII (6.5 g, 0.023 mole) the mixture was heated at 60–65° for 35 min and then cooled and triturated with ice water (100 ml). The orange-red product was removed by filtration, suspended in warm water (50 ml), and dissolved by the addition of 5% HCl (40 ml); concentrated HCl (2.5 ml) was added. The dark red hydrochloride salt that separated upon chilling was removed by filtration, dissolved in water (65 ml), filtered, diluted with an equal volume of isopropyl alcohol, and made basic (5% NaOH). The yield of XVIII that separated was 4 g (56%), mp 212–214°.

Anal. Calcd for $C_{15}H_{17}N_7O$: C, 57.86; H, 5.51; N, 31.50. Found: C, 57.95; H, 5.54; N, 31.45.