pared by the catalytic hydrogenation of a solution of 400 mg (1.53 mmol) of **19** in 50 ml of EtOH and 150 mg of 10% Pd/C at room temperature. After the absorption of hydrogen ceased the reaction mixture yielded 320 mg (90%) of the product, mp 175–178°, which was identical with an authentic sample of o-aminoglutethimide.

2-(*p*-Hydroxyphenyl)-2-ethylglutarimide (18). A solution of 700 mg (3.3 mmol) of **16** in 20 ml of 2 *N* H_2SO_4 was cooled to 5° and diazotized with 480 mg (7 mmol) of $NaNO_2$ dissolved in 2 ml of H_2O at 5°. The solution of diazonium salt was then added dropwise to 10 ml of boiling H_2O and the solution was held at reflux for 1 hr and then allowed to cool. The reaction mixture was saturated with NaCl and extracted with CH_2Cl_2 (3 × 50 ml). The organic layer was dried ($MgSO_4$) and filtered and the solvent evaporated under reduced pressure. The oily residue was recrystallized from Et_2O to yield 470 mg (61%) of a white crystalline solid: mp 143–144°; ir (KBr) 3240 (OH, NH), 1710, 1680 cm^{-1} (C=O imide); NMR (DMSO-d_6) δ 0.86 (t, 3, CH_3CH_2), 1.68–2.33 (m, 6, CH_3CH_2 and 2-methylene glutarimide ring), 6.73 (d, 2, H_3 and H_5 arom protons, J = 8.8 Hz, typical A_2B_2 system of para-substituted benzene), 7.13 (d, 2, H_2 and H_6 arom protons, J = 8.8 Hz), 9.33 (s, 1, OH exchangeable with D_2O), 8.3 (s, 1, NH, exchangeable with D_2O); mass spectrum, M^+ 233. Anal. ($C_{13}H_{15}NO_3$) C, H, N.

Acknowledgments. A preliminary account of this work was presented to the Medicinal Chemistry Section, APHA 121st National Meeting, Chicago, Ill., August 1974. This investigation was supported by U.S. Public Health Service Grant GM 12675. We thank Dr. David E. Nichols for his suggestions and discussions during the preparation of this manuscript. The authors acknowledge Mr. Dennis Charkowski and Mr. Archie Jones for their technical assistance. An authentic sample of *p*-aminoglutethimide and *o*-aminoglutethimide was obtained from Dr. J. J. Clark, Ciba-Geigy Corp., Ardsley, N.Y. 10502.

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(25) R. D. Sofia, *J. Pharm. Sci.*, **58**, 900 (1969).
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(28) R. Paul, R. P. Williams, and E. Cohen, *J. Med. Chem.*, **17**, 539 (1974).

Synthesis and Antihypertensive Properties of New 3-Hydrazinopyridazine Derivatives

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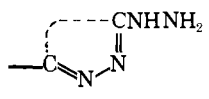
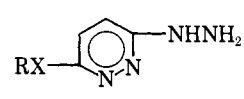
3-Hydrazinopyridazines substituted in position 6 with a primary amine, secondary amine, or an alkoxy group were synthesized and screened for antihypertensive activity. In general, the 6-dialkylamino derivatives are the most active; the (2-hydroxypropyl)methylamino chain provides the best combination of high antihypertensive activity and low toxicity.

The potent and long-lasting antihypertensive activity of hydrazinophthalazines,[1] exemplified by hydralazine and dihydralazine, encouraged the investigation of modified heterocyclic analogs[2] and particularly of six-membered rings containing the essential moiety A.[3] In the case of pyridazine series B, various 6-substituted derivatives with alkyl,[4] aryl,[5] methoxy,[6] phenoxy,[6] carbamyl,[7] and hydrazino[8] groups have been synthesized, but only few of them retained interesting hypotensive properties. Compounds of type B in which X is NR′, NH, or O had received little attention until a remarkable improvement in activity and decrease in toxicity was recently obtained by replacing RX with a secondary amino residue.[9,10] These results prompted us to undertake a more detailed study designed to define structure–activity relationships and to optimize activity in this class of 6-substituted 3-hydrazinopyridazines.

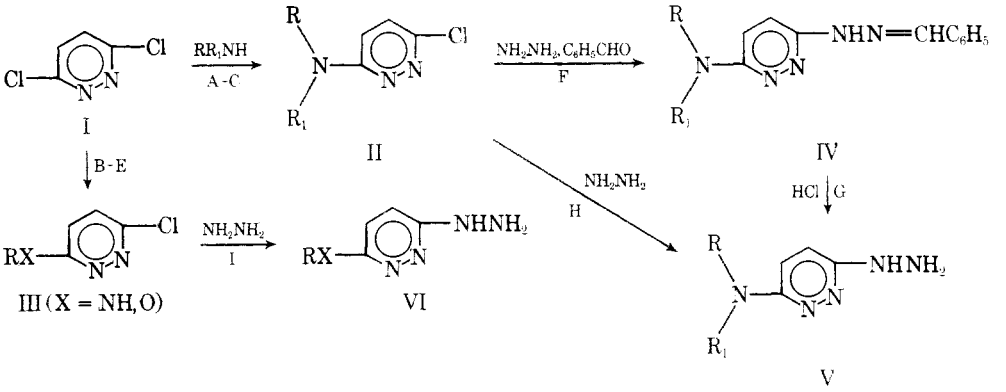


A



B (X = NR′, NH, O)

Scheme I

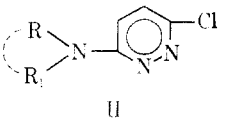


Chemistry. Scheme I depicts the synthetic routes employed for the preparation of 6-dialkylamino-, 6-aralkylamino-, and 6-cycloalkylamino-substituted 3-hydrazinopyridazines V. A conventional approach[11] involved displacement of one chlorine from 3,6-dichloropyridazine (I) with an appropriate secondary amine. The experimental conditions (see methods A–C) varied depending on the physicochemical properties and reactivity of organic bases. The resulting 6-amino-3-chloropyridazines II (Table I) were then heated with hydrazine; this reaction proved to be much more difficult than that of 6-unsubstituted derivatives due to the deactivating effect of the 6-amino group.[12] The hydrazines V could be directly isolated as hydrochlorides from the reaction mixture (method H), but this was satisfactory only in a few cases and on small-scale preparations, owing to high water solubility of the salts and the ensuing difficulties in the separation from hydrazine hydrochloride. A more efficient process involved formation of the hydrazones IV (Table III) with benzaldehyde (method F) followed by hydrolysis with hydrochloric acid to give the corresponding hydrochlorides (Table IV).

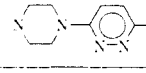
6-Alkoxy-3-hydrazinopyridazines (VI, Table V) were prepared by heating I in xylene with the appropriate sodium alkoxide (method D) to give III (X = O), with the exception of **20** which was obtained by heating I with *N*-(2-hydroxyethyl)aniline in anhydrous DMF in the presence of K_2CO_3 (method E). These intermediates **17–20** (Table II) were then allowed to react with hydrazine to afford the products (method I).

The 6-monoalkylamino-substituted compounds **21–24** (Table II) were prepared by heating I with the appropriate primary amine (methods B and C). Since the chlorine atom

Table I. 3-Chloro-6-dialkyl(cycloalkyl,aralkyl)aminopyridazines

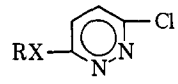


II

No.	-N(R)(R1)	Mp or bp (mm), °C	Method	Rxn temp, °C	Crystn solvent	Yield, %	Formula	Analyses
1	$N(CH_3)_2$	103–104[a]	A	80	*i*-Pr_2O	88	$C_6H_8ClN_3$	
2	$N(CH_3)(CH_2CH_2OH)$	66–67	B	105	Toluene	90	$C_7H_{10}ClN_3O$	Cl, N
3	Thiomorpholinyl	139–141	A	80	EtOH	80	$C_8H_{10}ClN_3S$	Cl, N, S
4	Piperazinyl	101–103	A	80	EtOAc	40	$C_8H_{11}ClN_4$	Cl, N
5	$N(C_2H_5)_2$	51–53[a]	C	150	*i*-Pr_2O	60	$C_8H_{12}ClN_3$	
6	$N(C_2H_5)(CH_2CH_2OH)$	136–138	B	110	*i*-PrOH	55	$C_8H_{12}ClN_3O$·HCl	Cl, N
7	$N(CH_3)(CH_2CHOHCH_3)$	82–83	B	105	EtOAc	95	$C_8H_{12}ClN_3O$	Cl, N
8	$N(C_2H_5)(CH_2CHOHCH_3)$	145–147	B	110	EtOH-Me_2CO	85	$C_9H_{14}ClN_3O$·HCl	Cl, N
9	$N(CH_2CH_2OH)(CH_2CHOHCH_3)$	69–71	B	140	EtOAc	68	$C_9H_{14}ClN_3O_2$	Cl, N
10	$N(CH_2CH{=}CH_2)_2$	138–140 (0.5)[b]	B	110		96	$C_{10}H_{12}ClN_3$	Cl, N
11		147–149	B	135	*i*-PrOH	35	$C_{10}H_{14}ClN_3O$·HCl	Cl, N
12		144–146	B	110	EtOH	50	$C_{10}H_{15}ClN_4O$	Cl, N
13	$N(CH_2CHOHCH_3)_2$	143–145	B	140	EtOAc	38	$C_{10}H_{16}ClN_3O_2$	Cl, N
14	$N(C_2H_5)(C_6H_5)$	199–201	B	140	*i*-PrOH	30	$C_{12}H_{12}ClN_3$·HCl	Cl, N
15	$N(CH_2CH_2OH)(C_6H_5)$	160–162	B	140	EtOH	25	$C_{12}H_{12}ClN_3O$·HCl	Cl, N
16		>300	A	80	DMF	30	$C_{12}H_{12}Cl_2N_6$	Cl, N

[a] Lit. mp 49–51°: R. Schönbeck and E. Klomstein, *Monatsh. Chem.*, 99, 15 (1968). [b] Oil which solidified on standing: Lit. mp 43–46°: P. L. Anderson, W. J. Houlihan and R. E. Manning, German Offen. 2.002.107 (1970); *Chem. Abstr.*, 73, 66596z (1970).

Table II. 3-Chloro-6-alkoxy(alkylamino)pyridazines



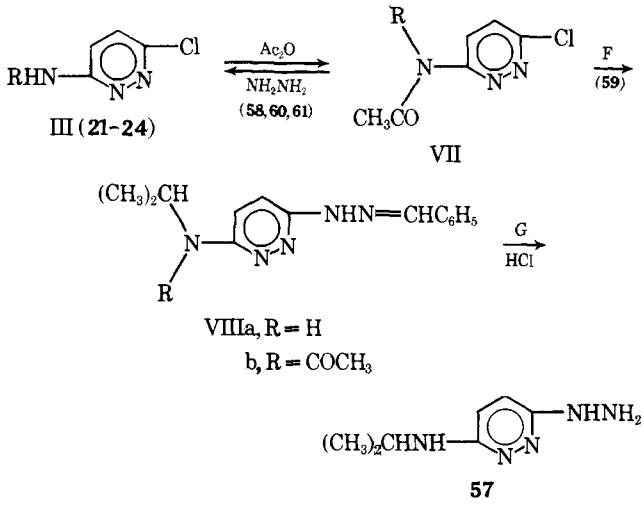
III

No.	R	X	Mp, °C	Method	Rxn temp, °C	Crystn solvent	Yield, %	Formula	Analyses
17	C_2H_5	O	59–61[a]	D	80	Petr ether	62	$C_6H_7ClN_2O$	
18	$(CH_3)_2NCH_2CH_2CH_2$	O	201–203	D	60	EtOH	30	$C_9H_{14}ClN_3O\cdot HCl$	Cl, N
19	$(C_2H_5)_2NCH_2CH_2$	O	181–183[b]	D	60	EtOH	32	$C_{10}H_{16}ClN_3O\cdot HCl$	Cl, N
20	$C_6H_5NHCH_2CH_2$	O	99–101	E	100	EtOH	50	$C_{12}H_{12}ClN_3O$	Cl, N
21	$HOCH_2CH_2$	NH	133–135[c]	B	105	H_2O	78	$C_6H_8ClN_3O$	
22	$(CH_3)_2CH$	NH	114–116[d]	C	110	i-Pr_2O	88[d]	$C_7H_{10}ClN_3$	
23	$(CH_3)_2NCH_2CH_2CH_2$	NH	129–131	B	105	CH_2Cl_2	58	$C_9H_{15}ClN_4$	Cl, N
24	$(C_2H_5)_2NCH_2CH_2$	NH	80–82	B	110	i-Pr_2O	80	$C_{10}H_{17}ClN_4$	Cl, N

[a] Lit.[17] mp 62°. [b] Lit. bp 190–200° (4 mm) for free base: T. Itai and H. Igeta, *J. Pharm. Soc. Jpn.*, 74, 1195 (1954); *Chem. Abstr.*, 49, 14768c (1955). [c] M. Kumagai, *Nippon Kagaku Zasshi*, 82, 227 (1961); *Chem. Abstr.*, 56, 10139h (1962). [d] Lit. 62% yield and mp 110–112°: D. I. Relyea, J. A. Riddel, and P. O. Tawney, *J. Med. Chem.*, 6, 807 (1963).

of compounds **21–24** could not be displaced by hydrazine,[13] these compounds were converted (Scheme II) with acetic anhydride into the corresponding acetyl derivatives (VII, Table VI) to reactivate the halogen atom. Reaction of **59** with hydrazine and subsequently with benzaldehyde (method F) afforded VIIIa or VIIIb depending on the reaction conditions. Hydrolysis of VIIIb with hydrochloric acid provided 3-hydrazino-6-isopropylaminopyridazine (**57**). However, treatment of compounds **58, 60,** and **61** with hydrazine under various conditions resulted in preferential hydrolysis of the amide linkage. The structures of most compounds (II–VIII) were supported by spectroscopic data (ir and NMR).

Scheme II



Pharmacology. The hypotensive activity of compounds **39–57** was assessed in chloralose–urethane anaesthetized cats; blood pressure was continuously measured by a mercury manometer and the compounds were administered by iv route. The antihypertensive activity was determined in unanaesthetized renal hypertensive rats;[14] the compounds were given by gavage and systolic blood pressure was measured by an indirect method[15] before and at 1, 3, 5, 7, and 24 hr after treatment. The activity on blood pressure, determined in the two above tests, was expressed as ED_{20} (i.e., the dose producing a 20% pressure drop from basal value). At least three dose levels for each compound were used producing 10–50% pressure drop and three to four animals were used for each dose level.

The approximate ip LD_{50} was determined in mice. Six dose levels were used and mortality in 7 days was recorded.[16]

Hydralazine was used as the reference drug. The results of the biological tests are given in Table VII.

The following conclusions on structure–activity relationships of 3-hydrazino-6-aminopyridazines V can be drawn. (1) Cycloalkylamino derivatives are slightly more potent (**41** and **52**) or less toxic (**48**) than hydralazine. (2) Aralkylaminopyridazines (**50** and **51**) present no advantage with respect to potency or toxicity. (3) Dialkylamino derivatives (**39, 40, 42–47,** and **49**) are the most interesting compounds. Some (**39, 40, 42, 43,** and **47**) display potent antihypertensive activity with only negligible change of toxicity as compared to hydralazine. Other derivatives (**46** and **49**) are as active as hydralazine but considerably less toxic. Compounds **44** and **45** display both high potency and low toxicity. These findings suggest that the presence of secondary alcoholic groups in this series may account for the low toxicity, while the high activity may be attributed to the lipophilic chain.

Further pharmacological evaluation of compound **44** showed that in renal hypertensive dogs it displays an antihypertensive action even at the dose of 0.1 mg/kg po. Haemodynamics studies in anaesthetized dogs revealed that it reduces peripheral resistances and increases aortic, femoral, and coronary blood flow. This compound is presently undergoing clinical studies in man.

In the 3-hydrazino-6-alkoxypyridazine series our results suggest that substitution with oxygen at position 6 may lead to compounds with lower toxicity.

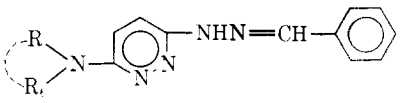
Experimental Section

Melting points were determined with a Büchi capillary apparatus and are uncorrected. All compounds were identified by NMR and ir spectroscopy. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

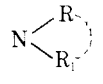
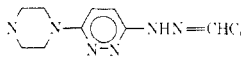
6-Substituted 3-Chloropyridazines II and III. Method A. 3-Chloro-6-(tetrahydro-1,4-thiazino)pyridazine (3). A mixture of 8.7 g (58 mmol) of 3,6-dichloropyridazine and 12 g (116 mmol) of tetrahydro-1,4-thiazine in 45 ml of EtOH was refluxed for 3 hr and then evaporated in vacuo to dryness. The residue was triturated with H_2O, filtered, and recrystallized to give 10 g of **3**.

Method B. 3-Chloro-6-[(2-hydroxyethyl)methylamino]pyridazine (2). To 90 g (1.2 mol) of (2-hydroxyethyl)methylamine

Table III. 3-Benzylidenehydrazino-6-alkyl(cycloalkyl,aralkyl)aminopyridazines

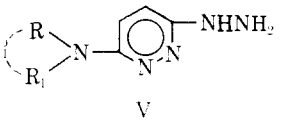


IV

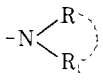
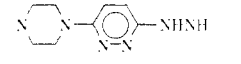
No.		Mp, °C	Crystn solvent	Yield, %	Formula	Analyses
25	$N(CH_3)_2$	229–232	EtOH[a]	12	$C_{13}H_{15}N_5$	C, H, N
26	$N(C_2H_5)_2$	202–205[b]	MeOH	15	$C_{15}H_{19}N_5$	C, H, N
27	$N(C_2H_5)(CH_2CH_2OH)$	195–198	EtOH[a]	27	$C_{15}H_{19}N_5O$	C, H, N
28	$N(CH_3)(CH_2CHOHCH_3)$	230–232 dec	*i*-PrOH	23	$C_{15}H_{19}N_5O \cdot HCl$	Cl, N
29	$N(C_2H_5)(CH_2CHOHCH_3)$	155–157	EtOH (80%)	25	$C_{16}H_{21}N_5O$	C, H, N
30	$N(CH_2CH_2OH)(CH_2CHOHCH_3)$	168–170	MeOH	30	$C_{16}H_{22}N_5O_2$	C, H, N
31	$N(CH_2CH{=}CH_2)_2$	173–175	EtOH	37	$C_{17}H_{19}N_5$	C, H, N
32	$c\text{-}N(CH_2CH_2)_2NCH_2CH_2OH$	240–243	EtOH	13	$C_{17}H_{22}N_6O$	C, H, N
33	$N(CH_2CHOHCH_3)_2$	184–187	EtOH[a]	32	$C_{17}H_{23}N_5O_2$	C, H, N
34	$N(C_2H_5)(C_6H_5)$	202–204	EtOH	30	$C_{19}H_{19}N_5$	C, H, N
35	$N(CH_2CH_2OH)(C_6H_5)$	199–201	EtOH[a]	58	$C_{19}H_{19}N_5O$	C, H, N
36	$N(CH_2CH_2OH)(CH_2C_6H_5)$	224–226	Dioxane	16	$C_{20}H_{21}N_5O$	C, H, N
37	$N(CH_2C_6H_5)CH_2CH_2N(C_2H_5)_2$	181–183	EtOH	26	$C_{24}H_{30}N_6$	C, H, N
38		315–319 dec	AcOH	13	$C_{26}H_{26}N_{10}$	C, H, N

[a] Hydrazine monohydrate was used rather than the anhydrous reagent. [b] Lit. mp 197–203°: E. Bellasio and G. Maffii, S. African Patent 67 07,803 (1968); *Chem. Abstr.*, 70, 68395h (1969).

Table IV. 3-Hydrazino-6-dialkyl(cycloalkyl,aralkyl)aminopyridazines



V

No.		Mp, °C[a,b]	Method	Yield, %	Formula	Analyses
39	$N(CH_3)_2$	233–235	G	88	$C_6H_{11}N_5 \cdot 2HCl$	C, H, N; Cl[c]
40	$N(CH_3)(CH_2CH_2OH)$	210–212	H	12	$C_7H_{13}N_5O \cdot 2HCl$	C, H, Cl, N
41	Thiomorpholinyl	212–214	H	38	$C_8H_{13}N_5S \cdot 2HCl$	C, H, Cl, N
42	$N(C_2H_5)_2$	234–236	G	80	$C_8H_{15}N_5 \cdot 2HCl$	C, H, Cl, N
43	$N(C_2H_5)(CH_2CH_2OH)$	193–195	G	67	$C_8H_{15}N_5O \cdot 2HCl$	C, H, Cl, N
44	$N(CH_3)(CH_2CHOHCH_3)$	206–209	G	85	$C_8H_{15}N_5O \cdot 2HCl$	C, H, Cl, N
45	$N(C_2H_5)(CH_2CHOHCH_3)$	208–210	G	92	$C_9H_{17}N_5O \cdot 2HCl$	C, H, Cl, N
46	$N(CH_2CH_2OH)(CH_2CHOHCH_3)$	178–180	G	40	$C_9H_{17}N_5O_2 \cdot 2HCl$	C, H, Cl, N
47	$N(CH_2CH{=}CH_2)_2$	214–217[d]	G	75	$C_{10}H_{15}N_5 \cdot 2HCl$	C, H, Cl, N
48	$c\text{-}N(CH_2CH_2)_2NCH_2CH_2OH$	240–242	G	90	$C_{10}H_{18}N_6O \cdot 3HCl$	C, H, Cl, N
49	$N(CH_2CHOHCH_3)_2$	190–192	G	61	$C_{10}H_{19}N_5O_2 \cdot 2HCl$	C, H, Cl, N
50	$N(C_2H_5)(C_6H_5)$	221–223	G	65	$C_{12}H_{15}N_5 \cdot 2HCl$	C, H, Cl, N
51	$N(CH_2CH_2OH)(C_6H_5)$	190–192	G	82	$C_{12}H_{15}N_5O \cdot 2HCl$	C, H, Cl, N
52		257–259	G	68	$C_{12}H_{18}N_{10}$	C, H, N

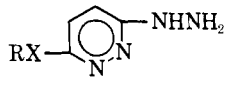
[a] With decomposition. [b] All compounds were recrystallized from EtOH, with the exception of 52 which was transformed in base and crystallized from H_2O. [c] Cl: calcd, 31.35; found, 30.25. [d] P. L. Anderson, W. J. Houlihan, and R. E. Manning, German Offen. 2.002.107 (1970); *Chem. Abstr.*, 73, 66596n (1970).

heated at 105°, 89.4 g (0.60 mol) of 3,6-dichloropyridazine was added with stirring in small portions over a period of 2 hr. When addition was complete, stirring was continued at 105–110° for 30 min; then the resulting brown mixture was dissolved in 80 ml of H_2O and continuously extracted with EtOAc for 20 hr. The organic extract was dried (Na_2SO_4) and the solvent evaporated. The residue was triturated with Et_2O, filtered, and recrystallized from toluene to yield 101 g of **2**.

Method C. 3-Chloro-6-diethylaminopyridazine (5). A mixture of 12 g (80.5 mmol) of 3,6-dichloropyridazine and 60 ml of anhydrous diethylamine was heated in a stainless bomb at 150° for 4 hr. After cooling, the excess of base was evaporated; the residue was taken up with H_2O, filtered, and crystallized to give **5**.

Method D. 3-Chloro-6-(3-dimethylaminopropoxy)pyridazine Hydrochloride (18). To 9.2 g (0.40 g-atom) of sodium in 140 ml of dry xylene, 45.5 g (0.44 mol) of 3-dimethylamino-1-propanol was slowly added and the mixture was heated to the reflux temperature until reaction was complete. The resulting solution was then cooled to 60° and a solution of 59.6 g (0.40 mol) of 3,6-dichloropyridazine in 100 ml of dry xylene was added with stirring

Table V. 3-Hydrazino-6-alkoxy- and -6-alkylaminopyridazines

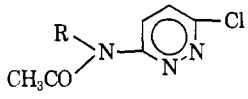


VI

No.	R	X	Mp, °C	Method	Crystn solvent	Yield, %	Formula	Analyses
53	C_2H_5	O	151–153	I	Me_2CO	15	$C_9H_{14}N_4O$[a]	C, H, N
54	$(CH_3)_2NCH_2CH_2CH_2$	O	210–212 dec	I	MeOH	23	$C_9H_{17}N_5O$·2HCl	C, H, Cl, N
55	$(C_2H_5)_2NCH_2CH_2$	O	201–203 dec	I	*i*-PrOH	24	$C_{10}H_{19}N_5O$·2HCl	C, H, Cl, N
56	$C_6H_5NHCH_2CH_2$	O	189–192 dec	I	EtOH	46	$C_{12}H_{15}N_5O$·2HCl	C, H, Cl; N[b]
57	$(CH_3)_2CH$	NH	225 dec	I	EtOH	14	$C_7H_{13}N_5$·2HCl	C, H, Cl, N

[a]Isolated as isopropylidene derivative. [b]N: calcd, 22.00; found, 22.94.

Table VI. 3-Chloro-6-(*N*-acetyl-*N*-alkylamino)pyridazines



VII

No.	R	Mp or bp (mm), °C	Crystn solvent	Yield, %	Formula	Analyses
58	$CH_3COOCH_2CH_2$	155–160 (0.5)[a]		95[b]	$C_{10}H_{12}ClN_3O_3$	Cl, N[c]
59	$(CH_3)_2CH$	96–99	*i*-Pr_2O	52	$C_9H_{12}ClN_3O$	C, H, Cl, N
60	$(CH_3)_2NCH_2CH_2CH_2$	152–154	EtOH	42	$C_{11}H_{17}ClN_4O$·HCl[d]	Cl, N
61	$(C_2H_5)_2NCH_2CH_2$	145 (0.25)		78	$C_{12}H_{19}ClN_4O$	C, H, Cl, N

[a]This compound partially decomposed by distillation on a bulb tube apparatus. An analytical sample was obtained by chromatography on silica gel ($CHCl_3$–MeOH, 9:1). [b]As crude material. [c]Cl: calcd, 13.76; found, 14.26. N: calcd, 16.30; found, 15.51. NMR peaks ($CDCl_3$, δ ppm) at 7.92 and 7.62 AB q (J = 9.1 Hz, 2 H pyridazine ring hydrogens), 4.33 br s (4 H, OCH_2CH_2N), 2.30 s (3 H, CH_3CON), 1.98 s (3 H, CH_3COO). [d]Prepared from the corresponding base in Me_2CO by adding ethereal HCl.

over a period of 15 min. After addition was complete, stirring was continued at the same temperature for 10 hr. The reaction mixture was cooled and extracted with dilute HCl. The aqueous phase was made basic with 50% NaOH and extracted with Et_2O. The ether solution was dried (Na_2SO_4) and treated with ethereal HCl. The precipitate was filtered and twice recrystallized from EtOH to give **18**·HCl.

Compound **17** was directly obtained from I and EtONa in EtOH according to the procedure of Takabayashi.[17]

Method E. 3-(2-Anilinoethoxy)-6-chloropyridazine Hydrochloride (20). A suspension of 2.98 g (20 mmol) of 3,6-dichloropyridazine, 3.76 g (27.4 mmol) of *N*-(2-hydroxyethyl)aniline, and 10.3 g (74.6 mmol) of finely powdered K_2CO_3 in 40 ml of anhydrous DMF was heated with stirring at 100° for 10 hr. After cooling, the insoluble salts were removed by filtration and the filtrate was evaporated to dryness in vacuo. The residue was taken up with $CHCl_3$, washed with H_2O, and dried (Na_2SO_4). The solvent was evaporated to dryness. The residue was triturated with Et_2O and crystallized from EtOAc to give 2.5 g (50%) of **20**, mp 98–101°.

Base (1 g) in EtOH was treated with dry HCl. The *hydrochloride* was filtered and recrystallized from EtOH.

3-Benzylidenehydrazino-6-aminopyridazines IV. Method F. 3-Benzylidenehydrazino-6-[*N*-(2-hydroxyethyl)-2-hydroxypropylamino]pyridazine (30). A mixture of 18.5 g (0.80 mol) of 3-chloro-6-[*N*-(2-hydroxyethyl)-2-hydroxypropylamino]pyridazine (**8**) and 125 ml of 95% hydrazine was gently refluxed with stirring for 3 hr under N_2. After cooling, the excess of hydrazine was removed in vacuo from the resulting solution (*caution!*). The residue was treated twice with EtOH and the solvent was evaporated in vacuo. The resulting oil was dissolved in 240 ml of EtOH, 35 ml of benzaldehyde and 24 g of finely powdered K_2CO_3 were added, and the mixture was refluxed for 2 hr. The solvent was evaporated in vacuo and the residue was taken up with Et_2O, filtered, and triturated with H_2O to remove the alkaline salts. The crude product was recrystallized from EtOH to yield 7.6 g of **30**.

Compound **25** was synthesized according to method F, but K_2CO_3 was not used. For compound **38**, AcOH was used as solvent for the crude hydrazino derivative instead of EtOH.

6-Amino-3-hydrazinopyridazines V. Method G. 3-Hydrazino-6-[*N*-(2-hydroxyethylanilino)]pyridazine Dihydrochloride (51). A stirred solution of 3-benzylidenehydrazino-6-[*N*-(2-hydroxyethylanilino)]pyridazine (**35**, 4.5 g, 13.5 mmol) in 150 ml of 15% HCl was refluxed and the benzaldehyde which formed was distilled off under N_2. Additional 15% HCl was used to keep the initial volume, and refluxing was continued until the hydrolysis was complete (~4 hr). The solution was evaporated to dryness in vacuo and the residue was taken up twice with EtOH and then evaporated. The dry residue was crystallized from EtOH to give 3.52 g of **51**.

Method H. 3-Hydrazino-6-(tetrahydro-1,4-thiazino)pyridazine Dihydrochloride (41). A mixture of 7.89 g (36.6 mmol) of 3-chloro-6-(tetrahydro-1,4-thiazino)pyridazine (**3**) and 75 ml of $NH_2NH_2·H_2O$ was refluxed for 4 hr and then cooled. The solution was evaporated to dryness in vacuo and the residue was crystallized from EtOH to give 3.4 g of **41** as the free base: mp 142–146°. The product was dissolved in CH_3OH and treated with methanolic HCl. The solvent was evaporated in vacuo and the residue was twice recrystallized from EtOH to afford 3.95 g of **41**.

3-Alkoxy-6-hydrazinopyridazines VI. Method I. 3-(2-Diethylaminoethoxy)-6-hydrazinopyridazine Dihydrochloride (55). A mixture of 8.0 g (35 mmol) of 3-chloro-6-(2-diethylaminoethoxy)pyridazine (**19**) as free base and 80 ml of $NH_2NH_2·H_2O$ in 35 ml of EtOH was refluxed for 5 hr and the resulting solution was evaporated in vacuo. The oil residue was taken up several times with EtOH and the solvent evaporated to remove the last traces of hydrazine hydrate. The resulting oil was dissolved in EtOH, cooled, and acidified to Congo Red with ethereal HCl. The solvent was evaporated in vacuo; the residue was taken up again in *i*-PrOH and concentrated in vacuo to dryness. The solid residue was heated in 140 ml of *i*-PrOH and filtered on Celite to remove some insoluble salts. The filtrate was cooled at 0° overnight to give 2.5 g of **55**.

3-(*N*-Acetyl-*N*-alkylamino)-6-chloropyridazines VII. (*N*-Acetyl-*N*-isopropylamino)-6-chloropyridazine (59). A mixture of 15 g (87.5 mmol) of 3-chloro-6-isopropylaminopyridazine (**22**) and 150 ml of Ac_2O was heated at 90° for 6 hr and the resulting

Table VII. Activity Data

No.	Anaesthetized cats[a] ED_{20},[c] mg/kg iv	Rel potency[d]	Renal hypertensive rats[b] ED_{20},[c] mg/kg po	Rel potency[d]	LD_{50}, mg/kg iv
39	0.01	10	2	5	50
40	0.02	5	1	10	150
41	0.03	3	3	3	100
42	0.01	10	0.5	20	80
43	0.02	5	2	5	150
44	0.02	5	1	10	600
45	0.03	3	1	10	600
46	0.1	1	20	0.5	1000
47	0.01	10	1.5	7	100
48	0.1	1	20	0.5	700
49	0.3	3	20	0.5	1000
50	0.1	1	5	2	100
51	0.04	2.5	5	2	100
52	0.05	2	5	2	150
53	0.05	2	5	2	100
54	0.1	1	5	2	700
55	0.1	1	5	2	700
56	0.07	0.7	5	2	80
57	0.1	1	1.5	7	150
Hydralazine	0.1	1	10.0	1	100

[a]Basal mean blood pressure, 130–150 mmHg. [b]Basal systolic blood pressure, 216 ± 2.9 (SD) mmHg (mean of 360 rats). [c]Dose producing a 20% pressure drop from basal value. The maximal effect was reached 20–30 min after administration in cats and 1–3 hr after administration in rats. [d]Ratio ED_{20} of hydralazine/ED_{20} of test compound.

dark solution was concentrated in vacuo. The residue was taken up with H_2O, made alkaline with 15% K_2CO_3, and extracted several times with $CHCl_3$. The combined extracts were washed with an aqueous solution of 5% HCl saturated with NaCl and then with a saturated NaCl solution and finally dried over Na_2SO_4. After evaporation, the solid residue was crystallized to give 9.5 g of **59**.

3-(*N*-Acetyl-*N*-isopropylamino)-6-benzylidenehydrazinopyridazine (VIIIb). Reaction of 3 g of **59** and 30 ml of 95% hydrazine at room temperature for 1 hr (method F) gave 1.55 g (37%) of VIIIb, mp 248–251° (from EtOH). Anal. ($C_{16}H_{19}N_5O$) C, H, N.

When the same reaction was performed at the reflux temperature for 2 hr, the *deacetyl* compound VIIIa was isolated in 15% yield: mp 202–204°. Anal. ($C_{14}H_{17}N_5$) C, H, N.

Reactions of compounds **58**, **60**, and **61** with 95% hydrazine under various conditions gave no condensation products and only the corresponding deacetylated derivatives **21**, **23**, and **24** were isolated from the reaction mixture.

3-Hydrazino-6-isopropylaminopyridazine dihydrochloride (57) was prepared by method G from VIIIb (10 g, 33.6 mmol) and 300 ml of 15% HCl and recrystallized from EtOH.

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Quinoxaline Studies. 23.[1a] Potential Antimalarials. Substituted 5,8-Dimethoxyquinoxalines[1b]

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Two series of 2,3-disubstituted 5,8-dimethoxy-6-[*N*-(ω-dimethylaminoalkyl)amino]quinoxalines were prepared: the first series with identical 2,3-substituents H, CH_3, C_6H_5, C_6H_4-4-Cl, and $CH_2C_6H_5$; and the second with identical styryl groups $CH{=}CHC_6H_5$, $CH{=}CHC_6H_4$-4-Cl, $CH{=}CHC_6H_3$-3,4-Cl_2, $CH{=}CHC_6H_4$-4-F, $CH{=}CHC_6H_4$-4-CF_3, and $CH{=}CHC_6H_4$-4-NO_2. None of the substances possessed antimalarial activity; several were toxic at highest dosage levels.

Previously reported[2] quinoxalinemethanols, unlike many quinolinemethanols, were without antimalarial capacity. It has been postulated[3–8] that the antimalarial activity of the quinoline compounds is due to quinoid materials formed in the host. It was hoped, therefore, that suitably substituted 5,8-dimethoxyquinoxalines would be especially easily transformed in vivo into the corresponding quinoxalinequinones, which might possess antimalarial qualities. And further, unpublished data related to earlier work[2] indicated that styryl derivatives of quinoxaline possessed some anti-