# Synthesis and Antihypertensive Activity of New 6-Heteroaryl-3-hydrazinopyridazine Derivatives

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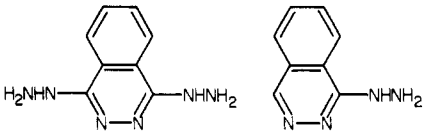
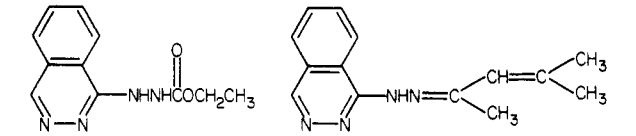
The synthesis and pharmacological activity of new 6-heteroaryl-3-hydrazinopyridazines with antihypertensive action are described. The introduction of pyrrole, pyrazole, imidazole, triazole, tetrazole, thiophene, indole, and carbazole heterocyclic rings into the 6 position of the pyridazine nucleus has been carried out by three different methods of synthesis. The hypotensive action has been examined on normotensive and spontaneously hypertensive rats by comparison with dihydralazine (I). 6-Imidazol-1-yl derivatives have proved particularly active. Of these derivatives, 3-hydrazino-6-(2-methylimidazol-1-yl)pyridazine (**7c**) achieves 4.9 times the activity of dihydralazine when administered orally to spontaneously hypertensive rats. The $LD_{50}$ values of **7c** and dihydralazine are very similar.

Vasodilators of the dihydralazine (I) or hydralazine (II)[1] type, having a peripheral action, are important agents in the pharmacotherapy of hypertension.[2,3,9]

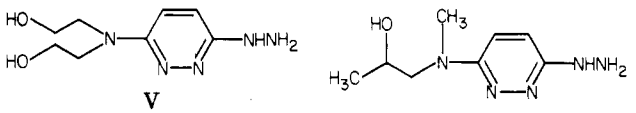


I II

Experiments carried out to improve these two hydrazinophthalazine derivatives in respect to their side effects, by structural modification, led to substances such as ecarazine (III),[4] budralazine (IV),[5] oxdralazine (V),[6] and propildazine (VI).[7]



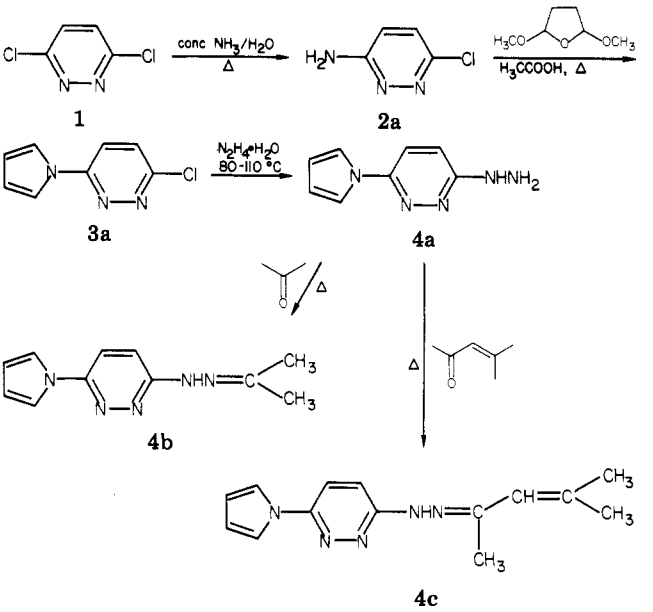
III IV



V VI

The object of our work was to develop new substances structurally similar to dihydralazine having a higher activity and a lower toxicity. In particular, it was intended to replace the alkylamino side radicals of V and VI by nitrogen-containing heterocyclic rings. Because of the closer analogy, the C–N linkage at the 6 position of the pyridazine nucleus was initially retained and the synthesis of new 6-*N*-heteroaryl-3-hydrazinopyridazine derivatives was carried out.

Scheme I



The following is an account of the introduction of a pyrrole, pyrazole, imidazole, triazole, indole, carbazole, or thiophene nucleus into the 6 position of the basic structure of 3-hydrazinopyridazine and of the hypotensive properties of the new compounds.

**Chemistry. (a) 3-Hydrazino-6-pyrrol-1-ylpyridazine Derivatives.** The synthesis of the 3-hydrazino-6-pyrrol-1-ylpyridazine derivatives **4a–c** is outlined in Scheme I. The melting points and yields are listed in Table I.

The reaction of 3,6-dichloropyridazine (**1**) with concentrated ammonia solution, at 100 °C in an autoclave, yielded 6-amino-3-chloropyridazine (**2a**).[12] This was reacted with

Table I. Molecular Formulas, Melting Points, and Yields of the 3-Hydrazino-6-pyrrol-1-ylpyridazines **4a–e**[a]

| compd | formula | mp, °C | yield, % |
|---|---|---|---|
| 4a·HCl | $C_8H_9N_5 \cdot HCl$ | 220–222 | 39[b] |
| 4b·HCl | $C_{11}H_{13}N_5 \cdot HCl$ | 163–165 | 88[c] |
| 4c·HCl | $C_{14}H_{17}N_5 \cdot HCl$ | 132–134 | 85[c] |
| 4d·HCl | $C_{10}H_{13}N_5 \cdot HCl$ | 204–207 | 30[b] |
| 4e | $C_8H_9N_5O$ | 240–242 | 33[d] |

[a] C, H, and N analyses were within ±0.4% of the theoretical values. [b] Relative to 2a. [c] Relative to 4a. [d] Relative to 2b.

(1) J. Druey and A. Marxer, *J. Med. Pharm. Chem.*, 1, 1 (1959); J. Druey and J. Tripod, in "Antihypertensive Agents", Academic Press, New York, 1967, pp 223–262; J. Druey and B. H. Ringier, *Helv. Chim. Acta*, **34**, 195 (1951).
(2) G. Leclerc, C. G. Wermuth, F. Miesch, and J. Schwartz, *Eur. J. Med. Chem.*, **11**, 107 (1976); W. P. Heilman, R. D. Heilman, J. A. Scozzie, R. J. Wayner, J. M. Gullo, and Z. S. Ariyan, *J. Med. Chem.*, **22**, 671 (1979).
(3) E. Bellasio, F. Parravicini, and E. Testa, *Farmaco*, **24**, 919 (1969); E. Bellasio, A. Ripamonti, F. Parravicini, and E. Baldoli, *ibid.*, **27**, 591 (1972); D. Libermann and A. Rouaix, *Bull. Soc. Chim. Fr.*, 1793 (1959).
(4) W. Reiterer and H. Czitober, *Arzneim.-Forsch.*, **27**, 2163 (1977).
(5) A. Akashi, T. Chiba, and A. Kasahara, *Eur. J. Pharmacol.*, **29**, 161 (1974).
(6) E. Baldoli, A. Sardi, V. Dezulian, M. Capellini, and G. Bianchi, *Arzneim.-Forsch.*, **23**, 1591 (1973).
(7) G. Pifferi, F. Parravicini, C. Carri, and L. Dorigotti, *J. Med. Chem.*, **18**, 741 (1975).
(8) T. Horie and T. Ueda, *Chem. Pharm. Bull.*, **11**, 114 (1963); T. Itai and T. Nakashima, *ibid.*, **10**, 936 (1962).

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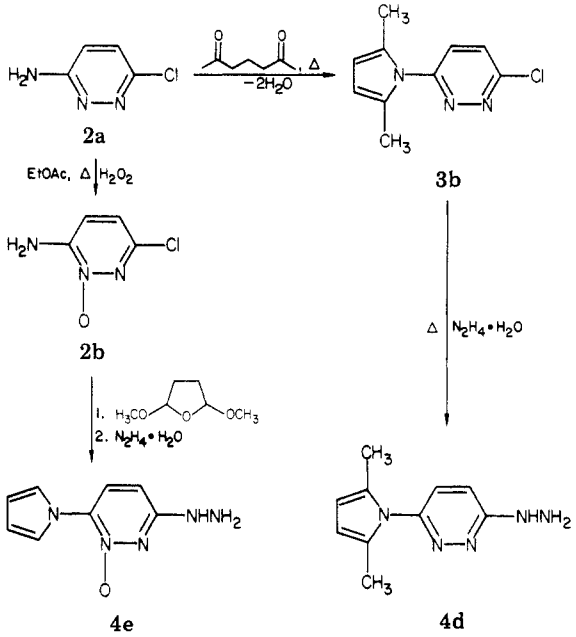
Table II. Molecular Formulas, Melting Points and Yields of the 3-Chloro-6-*N*-heteroarylpyridazines 6a–g and 6-*N*-Heteroaryl-3-hydrazinopyridazines 7a–g[a]

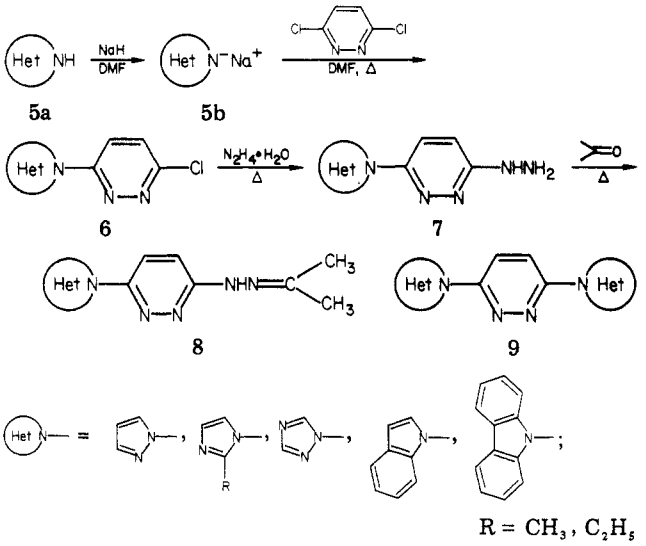
| no. | substituted pyridazine | formula | mp, °C | yield, % |
|---|---|---|---|---|
| 6a | 3-chloro-6-pyrazol-1-yl- | $C_7H_5ClN_4$ | 124–126 | 53 |
| 6b | 3-chloro-6-(imidazol-1-yl)- | $C_7H_5ClN_4$ | 178–180 | 49 |
| 6c | 3-chloro-6-(2-methylimidazol-1-yl)- | $C_8H_7ClN_4$ | 125–127 | 42 |
| 6d | 3-chloro-6-(2-ethylimidazol-1-yl)- | $C_9H_9ClN_4$ | 92–93 | 38 |
| 6e | 3-chloro-6-(1,2,4-triazol-1-yl)- | $C_6H_4ClN_5$ | 175–177 | 48 |
| 6f | 3-chloro-6-indol-1-yl- | $C_{12}H_8ClN_3$ | 165–166 | 31 |
| 6g | 3-chloro-6-carbazol-5-yl- | $C_{16}H_{10}ClN_3$ | 159–161 | 26 |
| 7a | 3-hydrazino-6-pyrazol-1-yl- | $C_7H_8N_6$ | 192–194 | 51 |
| 7b | 3-hydrazino-6-(imidazol-1-yl)- | $C_7H_8N_6$ | 199–202 | 63 |
| 7c | 3-hydrazino-6-(2-methylimidazol-1-yl)- | $C_8H_{10}N_6$ | 154–156 | 76 |
| 7d[b] | 3-hydrazino-6-(2-ethylimidazol-1-yl)-[b] | $C_9H_{12}N_6$[b] | 94–97 | 89 |
| 7e | 3-hydrazino-6-(1,2,4-triazol-1-yl)- | $C_6H_7N_7$ | 237–240 | 52 |
| 7f | 3-hydrazino-6-indol-1-yl- | $C_{12}H_{11}N_5$ | 120–122 | 82 |
| 7g | 3-hydrazino-6-carbazol-5-yl- | $C_{16}H_{13}N_5$ | 195–197 | 85 |

[a] C, H, and N analyses were within ±0.4% of the theoretical values. [b] $\cdot 0.5H_2O$.

Scheme II




Scheme III




2,5-dimethoxytetrahydrofuran in boiling acetic acid to give 3-chloro-6-pyrrol-1-ylpyridazine (**3a**) in 51% yield. Subsequent hydrazinolysis with hydrazine hydrate, at 80 to 110 °C (standard conditions), gave the desired product, 3-hydrazino-6-pyrrol-1-ylpyridazine (**4a**), which was converted to the hydrochloride with a solution of hydrogen chloride in ether.

The free hydrazine **4a** was converted to the hydrazone derivatives **4b** and **4c** by heating in acetone and mesityl oxide.

Pyrroles substituted by lower alkyl groups in the 2 and 5 position were synthesized by the conventional Paal–Knorr synthesis, as shown in the example of 2,5-dimethylpyrrol-1-yl-3-hydrazinopyridazine (**4d**, Scheme II).

6-Amino-3-chloropyridazine (**2a**) is reacted with hexane-2,5-dione, in the presence of an acid catalyst and under the action of heat. The water formed is removed by azeotropic distillation. The substituted pyrrole derivative **3b** is formed in 56% yield, which gives the end product **4d** by heating with hydrazine hydrate at 80–110 °C.

**2a** was also converted to 6-amino-3-chloropyridazine 1-oxide (**2b**),[8] by reaction with hydrogen peroxide in acetic acid. Further reaction with 2,5-dimethoxytetrahydrofurane in boiling acetic acid and subsequent hydrazinolysis yielded 3-hydrazino-6-pyrrol-1-ylpyridazine 1-oxide (**4e**).

**(b) Other 6-*N*-Heteroaryl-3-hydrazinopyridazine Derivatives.** Scheme III shows a general synthetic scheme for the preparation of other 6-*N*-heteroaryl-3-hydrazinopyridazine derivatives, **7a–g**. Pyrazole,[9] imidazole, triazole, indole, and carbazole derivatives, which can be substituted by alkyl groups, can be used as N-heterocyclic compounds in this preparation. In this synthetic variation, the particular heterocyclic compound **5a**, which must be unsubstituted on the N atom, is converted to the corresponding alkali metal salt, **5b**, by reaction with a strong base. The alkali metal salt is then reacted (inverse addition) with 1 mol of 3,6-dichloropyridazine (**1**) in a polar solvent, under the action of heat to form the desired heteroaryl pyridazine **6**.

Alkali metal and alkaline earth metal hydrides have proven particularly suitable as strong bases for formation of heterocyclic salts of **5a**. This procedure gives the 3-chloro-6-*N*-heteroarylpyridazines, **6a–g**, and the 2:1 adduct **9**, which is always formed together with these pyridazines; as an impurity, **9** is best removed by column chromatography. Subsequent hydrazinolysis at 80 to 110 °C again

(9) During our work the following publications of Richter Gedeon appeared, which also relate to 3-hydrazino-6-(pyrazol-1-yl)-pyridazines: DOS 2831072 (Oct 25, 1977), DOS 2825906 (June 13, 1977); Summary: G. Szilagyi, E. Kasztreiner, L. Tardos, L. Jaszlits, E. Kosa, G. Cseh, P. Tolnay, and I. Kovacs-Szabo, *Eur. J. Med. Chem.*, 14, 439 (1979).

(10) J. W. Mason and D. L. Aldous, *Chem. Heterocycl. Compd.*, 28, 25 (1973).

(11) G. Bachmann, British Patent 1168291 (Oct 22, 1969).

(12) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Am. Chem. Soc.*, 76, 3225 (1954).

Table III. Pharmacological Activity of the 6-Heteroaryl-3-hydrazinopyridazines

| compd | hypotensive act. in anesthetized rats: $ED_{20}$,[a] μmol/kg iv or ip | hypotensive act. in anesthetized rats: rel potency | antihypertensive act. in conscious SH rats: $ED_{20}$,[a] μmol/kg po | antihypertensive act. in conscious SH rats: rel potency | $LD_{50}$ in mice, μmol/kg ip |
|---|---|---|---|---|---|
| 4a | 0.423 (0.329-0.545) | 1.06 | 40.1 (30.9-51.8) | 0.90 | 389 (335-451) |
| 4b | 4.65 | 0.10 | | | |
| 4c | 1.77 (1.45-2.15) | 0.25 | | | |
| 4d | 8.02 (6.61-9.65) | 0.06 | | | |
| 4e | >5.24 ip | <0.34 | | | |
| 7a | 0.830 (0.727-0.943) | 0.54 | 27.3 (18.1-41.0) | 1.32 | 387 (328-457) |
| 7b | 2.64 | 0.17 | | | 853 |
| 7c | 0.163 (0.112-0.238) | 2.75 | 7.42 (4.57-12.1) | 4.88 | 1016 (953-1132) |
| 7d | 0.313 (0.211-0.457) | 1.43 | 14.3 (9.56-21.2) | 2.52 | 765 (706-838) |
| 7e | 2.62 | 0.17 | | | 262 |
| 7f | 2.06 | 0.22 | | | 206 |
| 7g | >16.9 ip | <0.11 | | | |
| 8c | 0.242 (0.130-0.452) | 1.86 | 10.7 (7.09-16.1) | 3.37 | 430 (376-487) |
| 8d | 0.247 (0.133-0.459) | 1.82 | 10.2 (7.01-14.8) | 3.54 | 508 (430-594) |
| 14a | 0.410 (0.370-0.455) | 1.08 | | | 521 (453-599) |
| 14b | 9.51 ip | 0.19 | | | |
| dihydralazin | 0.449 (0.393-0.513) iv<br>1.78 (1.47-2.16) ip | 1.00<br>1.00 | 36.1 (29.9-43.4) | 1.00 | 1084 (984-1200) |

[a] Dose which lowered the normal arterial pressure in anesthetized, respectively, the increased pressure in SH rats by 20%, calculated from the linear regression between log dose and relative reduction of blood pressure.

yields the particular 6-heteroaryl-3-hydrazinopyridazines **7a–g**.

Table II contains the melting points and yields of **6a–g** and **7a–g**. The free hydrazines **7c,d** were converted to the hydrazone derivatives **8c,d** by heating in acetone.

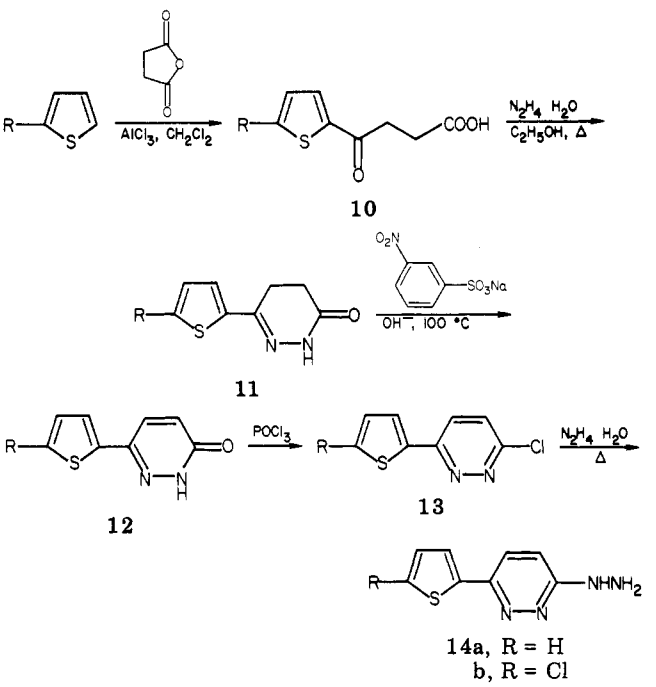
**(c) 3-Hydrazino-6-thien-2-ylpyridazine Derivatives 14a,b.** The synthesis of the 6-thien-2-ylpyridazine derivatives **14a,b** is outlined in Scheme IV.

The corresponding thiophene derivative was acylated in the 2 position, by means of a Friedel–Crafts reaction with succinic anhydride, to give the γ-ketocarboxylic acid **10**,[13] which was then cyclized with hydrazine hydrate to give 4,5-dihydro-6-thien-2-yl-3(2*H*)-pyridazinone (**11**). Dehydrogenation of **11** to give 6-thien-2-yl-3(2*H*)-pyridazinone (**12**) was initially very problematic because the normal procedure[10] of bromination, followed by subsequent elimination of HBr, led to bromination of the thiophene nucleus, and mixtures of diverse bromination products were obtained, which could not be further separated.

However, dehydrogenation of **11** to give **12** succeeded with the Na salt of *m*-nitrobenzenesulfonic acid in alkaline aqueous solution at 100 °C.[11]

Conversion to 3-chloro-6-thien-2-ylpyridazine was carried out with phosphorus oxychloride under the action of heat. Subsequent hydrazinolysis at 80–110 °C then gave the 3-hydrazino-6-thien-2-ylpyridazine derivatives **14a,b** with respective total yields of 28 and 17% and respective melting points of 89–92 and 195–198 °C (hydrate).

Scheme IV




## Results and Discussion

The hypotensive action in normotensive rats under urethane anesthesia was tested primarily in the pharmacological screening. Table III summarizes the results. Six of the 16 compounds tested showed an activity comparable to or above dihydralazine after intravenous or intraperitoneal administration. These active drugs also exhibited a high antihypertensive efficiency when administered orally in spontaneously hypertensive rats. The most potent compound (**7c**) is nearly five times as active as dihydralazine. In SH rats, the relative antihypertensive activity of most of the compounds tested is higher than in the experiments in anesthetized rats after parenteral administration, indicating that the enteral activity in SH rats is higher than that of dihydralazine.

Toxicity studies in mice showed similarity in the symptoms (moderate sedation, disorders in motor coordination, clonic seizures) and in the time course of intoxication after intraperitoneal administration of toxic doses. After lethal doses, most of the animals died within 2 h and only a few died within 24 h.

Obviously there is no correlation between acute toxicity ($LD_{50}$) and antihypertensive activity ($ED_{20}$). The most toxic compounds (**7e,f**) are less potent. Another substance (**7b**) with little activity is less toxic. Some relative potent substances such as **7c** and **7d** are less toxic, while some others such as **8c** and **8d**, are more toxic.

The replacement of the phthalazine ring system in dihydralazine by a pyridazine ring and the following sub-

(13) N. P. Buu-Hoï, N. Hoán, and N. D. Xuong, *Recl. Trav. Chim. Pays-Bas*, **69**, 1083 (1950); L. F. Fieser and R. G. Kenelly, *J. Am. Chem. Soc.*, **57**, 1611 (1935).

stitution of the hydrazine group in the 6 position by a heterocycle lead to different changes in the hypotensive activity and in the acute toxicity.

An analysis of the structure–activity relationships is only possible by use of the pharmacological data. In consideration of the small number of compounds, physicochemical parameters indicating electronic ($\sigma$) or steric (Es) influences of the different heterocycles in the 6 position are not available. In comparison with dihydralazine, the introduction of a pyrrolyl (**4a**) or a thienyl radical (**14a**) into the 6 position of the pyridazine ring does not influence the hypotensive or antihypertensive activity but increases the toxicity. A decrease of activity is seen by substitution with a pyrazolyl (**7a**) and especially with a triazolyl (**7e**), an indolyl (**7f**), or a carbazolyl radical (**7g**). These compounds, particularly **7a,e,f**, also are more toxic than dihydralazine.

Further substitution of the pyrrole, imidazole, or thienyl nucleus with alkyl or halogen is as well able to increase the hypotensive activity as to reduce it. The 2,5-dimethylpyrrolyl (**4d**) and the 5-chlorothienyl derivative (**14b**) are only active in high doses. On the other hand, in comparison with the nonalkylated derivative (**7b**) the introduction of alkyl substituents into the 2 position of the imidazole nucleus is accompanied by a remarkable increase in hypotensive activity. The 2-methyl derivative (**7c**) is 16 times as potent as **7b** and 2.75 times as potent as dihydralazine. Its toxicity is below that of **7b** and comparable with that of dihydralazine. The 2-ethylimidazolyl compound (**7d**) has only ca. 50% of the potency of the 2-methylimidazolyl (**7c**) but is still more potent than dihydralazine. It is a little more toxic than **7b**.

A comparison of the free hydrazines **7c** and **7d** with the corresponding isopropylidenehydrazones **8c** and **8d**, respectively, shows that the activity of the latter compounds is essentially unchanged but the toxicity is somewhat higher.

In the case of the unsubstituted pyrrolyl compounds, isopropylidenehydrazone (**4b**) and 2-methyl-2-penten-4-ylidenehydrazone (**4c**) are substantially less potent than the corresponding free hydrazine **4a**. Oxidation of the nitrogen in the 1 position of the pyridazine **4a** to give the *N*-oxide **4e** leads to a reduction in the hypotensive activity.

## Experimental Section

The following instruments were used to determine the physical properties of the compounds: $^1$H NMR, Perkin-Elmer R 24, Varian HA 60, XL 100, and 220, and Bruker WH 270 (internal standard tetramethylsilane); IR, Perkin-Elmer 521 (KBr disks); mass spectra, Atlas CH-4 (70 eV, direct injection) and Varian MAT CH-7 (70 eV, direct injection). Melting points (uncorrected) were determined using a Büchi melting point apparatus.

In the IR spectrum, the 6-heteroaryl-3-hydrazinopyridazines showed the characteristic broad NH absorption of the hydrazine group at 3000–3300 cm$^{-1}$ and also the aromatic bands of the particular heterocyclic rings in the 6 position. The $^1$H NMR spectrum showed the characteristic aromatic signals of the heterocyclic rings in the 6 position; the two doublets for the H atoms in the 4 and 5 position of the pyridazine nucleus were at $\delta$ 7.3–7.6 and 7.7–8.1, respectively, and showed the vicinal coupling constant of 8–10 Hz.

**3-Hydrazino-6-pyrrol-1-ylpyridazine (4a) Hydrochloride.** 3,6-Dichloropyridazine (1; 100 g, 671 mmol) in 1 L of concentrated aqueous ammonia solution was heated at 100 °C for 6 h in an autoclave under autogenous pressure. The 6-amino-3-chloropyridazine (**2a**),[12] which precipitated in the cold, was filtered off with suction and washed copiously with water. After drying, 42 g (49%) of **2a**, having a melting point of 234–236 °C dec, was isolated.

2,5-Dimethoxytetrahydrofuran (10.2 g) was added to 6-amino-3-chloropyridazine (2; 10.0 g, 78 mmol) in 30 mL of acetic acid, and the mixture was stirred for 45 to 60 min at 120 °C under nitrogen as a protective gas. After the mixture cooled, most of the 3-chloro-6-pyrrol-1-ylpyridazine (**3a**) crystallized out. The crystals were filtered off with suction and rinsed with a small amount of cold glacial acetic acid. After concentration to half the volume, the filtrate yielded a second fraction of product on cooling. The crude product was sufficiently pure for further reaction: yield 7.1 g (51%) of **3a** as colorless needles; mp 180–182 °C.

3-Chloro-6-pyrrol-1-ylpyridazine (**3a**; 7.1 g, 40 mmol) was taken up in 50 mL of hydrazine hydrate, and the mixture was stirred at 80 °C under nitrogen for 3 h. After the mixture cooled, it was poured into ice–water, and the precipitated solids were filtered off with suction and rinsed copiously with water. The crude product, having a melting point of 219–222 °C, was taken up in a small amount of hot ethanol, and the hydrochloride was precipitated with a solution of hydrogen chloride in ether: yield 6.5 g (77%) of 3-hydrazino-6-pyrrol-1-ylpyridazine (**4a**) hydrochloride; mp 220–222 °C. Anal. ($C_8H_9N_5$·HCl) C, H, N.

**3-(2-Isopropylidenehydrazino)-6-pyrrol-1-ylpyridazine (4b) Hydrochloride and 3-[2-(2-methyl-2-penten-4-ylidene)hydrazino]-6-pyrrol-1-ylpyridazine (4c) Hydrochloride.** 3-Hydrazino-6-pyrrol-1-ylpyridazine (2.0 g, 9.5 mmol) was suspended in 20 mL of acetone or mesityl oxide, and the suspension was warmed for 10 min on a steam bath. The hot solution was then filtered. When the solution cooled, the 3-(2-isopropylidenehydrazino)-6-pyrrol-1-ylpyridazine (**4b**), having a melting point of 214–215 °C, or the 3-[2-(2-methyl-2-penten-4-ylidene)hydrazino]-6-pyrrol-1-ylpyridazine (**4c**) crystallized out.

For conversion to the hydrochloride, a solution of hydrogen chloride in ether was added to the hot filtered reaction solution, and the hydrochloride was left to crystallize out in the cold: yield 2.1 g (88%) of **4b**·HCl, mp 163–165 °C, and 85% of **4c**·HCl, mp 132–134 °C. Anal. ($C_{11}H_{13}N_5$·HCl) C, H, N and ($C_{14}H_{17}N_5$·HCl) C, H, N.

**3-Hydrazino-6-(2,5-dimethylpyrrol-1-yl)pyridazine (4d) Hydrochloride.** 6-Amino-3-chloropyridazine (**2a**; 5.0 g, 39 mmol) in 100 mL of absolute toluene was refluxed for 3 h, via a Dean–Stark apparatus, with 5.1 g (45 mmol) of 2,5-hexanedione and also a catalytic amount of *p*-toluenesulfonic acid. Workup was carried out in the customary manner by washing the organic phase with water and 10% sodium bicarbonate solution, drying, and concentrating. 3-Chloro-6-(2,5-dimethylpyrrol-1-yl)pyridazine (**3b**; 4.5 g, 56%), having a melting point of 98–101 °C, was isolated, and this was sufficiently pure for the subsequent reaction with hydrazine hydrate.

The hydrazinolysis of **3b** and the conversion to the hydrochloride were carried out as described above. Fifty-three percent of 3-hydrazino-6-(2,5-dimethylpyrrol-1-yl)pyridazine (**4d**) hydrochloride, having a melting point of 204–207 °C, was isolated. Anal. ($C_{10}H_{13}N_5$·HCl) C, H, N.

**3-Hydrazino-6-pyrrol-1-ylpyridazine 1-Oxide (4e).** 2,5-Dimethoxytetrahydrofuran (3.6 g) was added to 4.0 g (28 mmol) of 6-amino-3-chloropyridazine 1-oxide (**2b**)[9] in 50 mL of acetic acid and 3 mL of water, and the mixture was stirred for 1.5 h at 120 °C under nitrogen. After the solvent was drawn off under reduced pressure, the residual crude product was recrystallized from ethanol. Forty-three percent of 3-chloro-6-pyrrol-1-ylpyridazine 1-oxide, having a melting point of 134–136 °C, was isolated, and this was stirred in 15 mL of hydrazine hydrate for 6 h at 80 °C under nitrogen. After cooling, the mixture was poured into ice–water, and the precipitated solids were filtered off with suction and rinsed copiously with water. After this was digested in hot ethanol and filtered with suction, 76% of 3-hydrazino-6-pyrrol-1-ylpyridazine 1-oxide (**4e**), having a decomposition point of 240–242 °C, was isolated. Anal. ($C_8H_9N_5O$) C, H, N.

**General Instructions for the Preparation of 3-Chloro-6-*N*-heteroarylpyridazines, 6a–g, Using 3-Chloro-6-(2-methylimidazol-1-yl)pyridazine (6c) as the Example.** A 55% suspension of sodium hydride (4.6 g, 104 mmol) in paraffin oil was added in portions to 8.55 g (104 mmol) of 2-methylimidazole in 80 mL of dimethylformamide, while stirring, and the 2-methylimidazole was converted to the sodium salt by subsequently stirring for 1 h at room temperature under nitrogen as a protective gas. This sodium salt solution was then added in portions to 15.5 g (104 mmol) of 3,6-dichloropyridazine in 70 mL of dimethylformamide, while stirring and cooling with an ice bath (exothermic reaction, temperature increases to 30 °C), and the mixture was

stirred at room temperature 12 h. The solvent was distilled off in an oil pump vacuum at about 0.5 mmHg, the residue was taken up in 3–4 L of ice–water, the aqueous phase was extracted with 1–2 L of methylene chloride, and the organic phase was washed several times with water. The byproduct, 3,6-bis(2-methylimidazol-1-yl)pyridazine, of the general formula **9** (polar component) was removed from the resulting crude mixture by column chromatography (silica gel; solvent system: 90:10 methylene chloride/methanol): yield 8.5 g (42%) of **6c** as crystals; mp 125–127 °C after recrystallization from ethyl acetate.

The other 3-chloro-6-*N*-heteroarylpyridazines, **6** (see Table II), were prepared in a similar manner.

**General Instructions for the Preparation of 6-*N*-Heteroaryl-3-hydrazinopyridazines, 7a–g, Using 3-Hydrazino-6-(2-methylimidazol-1-yl)pyridazine (7c) as the Example.** 3-Chloro-6-(2-methylimidazol-1-yl)pyridazine (6.7 g, 35 mmol) was taken up in 30 mL of hydrazine hydrate, and the mixture was heated at 100 to 130 °C for 5 to 10 h under nitrogen as a protective gas, the reaction mixture becoming homogeneous in the course of the first few hours. After cooling, the mixture was poured into 0.5 L of ice–water, and extraction was carried out several times with methylene chloride. Continuous extraction of the aqueous phase in a 1-L rotary perforator with methylene chloride or chloroform for 1–2 days proved the most effective method. The crude 3-hydrazino-6-(2-methylimidazol-1-yl)-pyridazine (**7c**) was purified by column chromatography (silica gel; solvent system 90:10 methylene chloride/methanol) and converted to the hydrochloride in ethanolic solution with a solution of hydrogen chloride in ether: yield 7.0 g (76%) of **7c**·2HCl; mp 280–282 °C dec. The free base **7c** melted at 154–156 °C. Anal. ($C_8H_{10}N_6$·2HCl) C, H, N, Cl.

The other 6-*N*-heteroaryl-3-hydrazinopyridazines, **7** (see Table II), were prepared in a similar manner.

**3-(2-Isopropylidenehydrazino)-6-(2-methylimidazol-1-yl)pyridazine (8c) and 3-(2-Isopropylidenehydrazino)-6-(2-ethylimidazol-1-yl)pyridazine (8d).** 3-Hydrazino-6-(2-methylimidazol-1-yl)pyridazine (**7c**; 3.0 g, 15.8 mmol) or 3-hydrazino-6-(2-ethylimidazol-1-yl)pyridazine (**7d**; 3.0 g, 14.7 mmol) was suspended in 40 mL of acetone, and the suspension was warmed on a steam bath for 10 min. The hot solution was then filtered. When the solution cooled, the 3-(2-isopropylidenehydrazino)-6-(2-methylimidazol-1-yl)pyridazine (**8c**) or 3-(2-isopropylidenehydrazino)-6-(2-ethylimidazol-1-yl)pyridazine (**8d**), having a melting point of 173–175 or 155–156 °C, respectively, crystallized out. Anal. ($C_{11}H_{14}N_6$) C, H, N and ($C_{12}H_{16}N_6$) C, H, N.

**3-Hydrazino-6-(5-chlorothien-2-yl)pyridazine (14b; R = Cl).** Five milliliters of hydrazine hydrate was added to 20.0 g (91.5 mmol) of 3-(5-chlorothienoyl)propionic acid (**10b**)[13] in 330 mL of ethanol, and the mixture was refluxed for 2 to 7 h. The yellowish reaction product precipitated during the reaction and, after cooling, was filtered off with suction and rinsed thoroughly with water. Recrystallization from ethanol yielded 17.3 g (88%) of 4,5-dihydro-6-(5-chlorothien-2-yl)-3(2*H*)-pyridazinone (**11b**), mp 258–260 °C.

The sodium salt of *m*-nitrobenzenesulfonic acid (11.3 g) and sodium hydroxide (7.6 g) was added to 14.0 g (65.2 mmol) of 4,5-dihydro-6-(5-chlorothien-2-yl)-3(2*H*)-pyridazinone (**11b**) in 240 mL of water, and the mixture was heated to 100 °C. While the mixture was being stirred thoroughly, ethanol was then added until the starting material had completely dissolved. After heating at 100 °C for 2 h, the hot reaction solution was filtered and the filtrate was weakly acidified with concentrated hydrochloric acid. The crude product which precipitated on cooling was filtered off with suction and recrystallized from ethanol: yield 11.8 g (86%) of 6-(5-chlorothien-2-yl)-3(2*H*)-pyridazinone (**12b**), mp 262–264 °C.

Fifty milliliters of phosphorus oxychloride was added to 5.0 g (24 mmol) of 6-(5-chlorothien-2-yl)-3(2*H*)-pyridazinone (**12b**), and the mixture was stirred at 135 °C for 1.5 h. The mixture was then poured onto ice–water, and extraction was carried out several times with methylene chloride. After the organic phase was washed, dryed, and concentrated in the customary manner, the crude product was recrystallized from ethanol. This yielded 3.2 g (58%) of 3-chloro-6-(5-chlorothien-2-yl)pyridazine (**13b**), mp 208–210 °C.

3-Chloro-6-(5-chlorothien-2-yl)pyridazine (**13b**; 3.0 g, 13 mmol) was suspended in 25 mL of hydrazine hydrate, and the suspension was refluxed for 3 h. After cooling, the mixture was then poured into ice–water, and the precipitated solids were filtered off with suction while rinsing copiously with water. The resulting crude product was recrystallized from ethanol. 3-Hydrazino-6-(5-chlorothien-2-yl)pyridazine (**14b**; 2.4 g, 75%), which was in the form of the hydrate having a melting point of 195–198 °C, was isolated. Anal. ($C_8H_7ClN_4S$·$H_2O$) C, H, N, S.

**3-Hydrazino-6-thien-2-ylpyridazine (14a; R = H)** was prepared in a corresponding manner.

**4,5-Dihydro-6-thien-2-yl-3(2*H*)-pyridazinone (11a)**: yield 85%; mp 118–120 °C.

**6-Thien-2-yl-3(2*H*)-pyridazinone (12a)**: yield 83%; mp 172–175 °C.

**3-Chloro-6-thien-2-ylpyridazine (13a)**: yield 68%; mp 157–159 °C.

**3-Hydrazino-6-thien-2-ylpyridazine (14a)**: yield 85%; mp 89–92 °C. Anal. ($C_8H_8N_4S$·$0.8H_2O$) C, H, N, S.

**Pharmacological Experiments. Hypotensive Activity in Anesthetized Rats.** Groups of five male normotensive Sprague–Dawley rats (230–280 g) under urethane anesthesia (1.78 g/kg ip) were used in the experiments. The substances were administered intravenously in a cannulated jugular vein or, in the case of poor solubility in $H_2O$, intraperitoneally as tragacanth suspensions (0.5 g of tragacanth in 100 mL of $H_2O$). The mean pressure in the carotid artery was measured with a Statham P 23 Db transducer. From the linear regressions between log dose ($\mu$mol/kg) and relative reduction of blood pressure ($\Delta$%), the dose which lowered the blood pressure by 20% was calculated as $ED_{20}$.

**Antihypertensive Activity in Conscious SH Rats.** The substances were administered orally to groups of four to eight male spontaneously hypertensive rats (280–350 g). The systolic blood pressure was determined using a tail-cuff method at an ambient temperature of 35 °C before and 2 h after administration of the substances. The blood pressure reduction ($\Delta$%) was determined in comparison to untreated animals. The $ED_{20}$ was calculated in the same manner as in the normotensive rats.

**Acute Toxicity in Mice.** The substances were administered intraperitoneally to groups of 10 female NMRI mice (19–26 g). The period of observation was 7 days. The $LD_{50}$ was evaluated by means of the probit analysis. Dihydralazine (1,4-dihydrazinophthalazine) was used as the reference substance.

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