reaction mixture was then treated with hydrogen gas at 40 psi in a Parr hydrogenation apparatus for 16 h at room temperature. The mixture was filtered through a Celite pad, and the pad was then washed with boiling water (50 mL). The filtrate was concentrated in vacuo to a volume of 5 mL, applied to a preparative thick-layer chromatographic plate, and then developed with methanol/chloroform (1:9, v/v). The main product (R_f 0.2) was collected by extraction of the silica gel with boiling methanol (100 mL). Evaporation of the methanol under reduced pressure gave **32** as a homogeneous oil: yield 60 mg (0.26 mmol, 70%). Crystallization of a small sample from methanol yielded an analytical sample, mp 145–146 °C. Anal. ($C_9H_{13}N_3O_4$) C, H, N.

5-Chloro-4-methoxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)pyridazin-6-one (31). Nucleoside **28** (2 g, 3.87 mmol) was dissolved in a mixture of methanol (50 mL) and tetrahydrofuran (35 mL). Sodium methoxide (300 mg, 5.6 mmol) was added, and the reaction mixture was stirred for 24 h at room temperature. Amberlite IR-120 resin (2 g, H^+ form) was added, and the mixture was stirred for an additional 3 h. The mixture was filtered and the resin was washed with boiling methanol (100 mL). The combined methanol washings were evaporated under reduced pressure to an oily mixture. Ethyl acetate (100 mL) and methanol (20 mL) were added to the mixture, and the solution was stored at 5 °C. After 2 h, the precipitated salts were removed by filtration, and the filtrate was concentrated to an oil. This oil was crystallized from chloroform (25 mL) to give **31** as a white powder: yield 850 mg (3.07 mmol, 79%); mp 154–156 °C. Anal. ($C_{10}H_{13}ClN_2O_5$) C, H, N.

4-Methoxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-pyridazin-6-one (33). Nucleoside **31** (500 mg, 1.18 mmol) was dissolved in methanol (100 mL) which contained 1.5 mL of 1 N sodium hydroxide. The reaction mixture was cooled to 5 °C and thoroughly purged with nitrogen. Palladium on carbon catalyst (10%; 200 mg) was added, and the mixture was then treated with hydrogen gas (40 psi) in a Parr hydrogenation apparatus for 13 h at room temperature. The reaction mixture was boiled and filtered through a Celite pad, and the pad was washed with boiling methanol (100 mL). The combined filtrates were concentrated under reduced pressure to an oil, which was triturated with ethanol (50 mL) at room temperature for 20 h. After filtration, the ethanol filtrate was coevaporated with 2 g of silica gel. This silica gel was then applied to an open-bed column (4.5 × 10 cm), and elution was performed with methanol/chloroform (1:19, v/v). Collecting 15-mL fractions, the product was eluted in fractions 30 through 50. These fractions were combined and then evaporated under reduced pressure to an oil, which was crystallized from cyclohexane to yield **33** as beige crystals: yield 260 mg (1.07 mmol, 59%); mp 122–124 °C. Anal. ($C_{10}H_{14}N_2O_5$) C, H, N.

4-Hydroxy-1-(2-deoxy-β-D-*erythro*-pentofuranosyl)-pyridazin-6-one (34, 6-Aza-3-deaza-2′-deoxyuridine). Potassium hydroxide (2 g) was dissolved in distilled water (10 mL). Nucleoside **33** (400 mg, 1.65 mmol) was added, and the mixture was heated at reflux for 1 h. The reaction mixture was cooled to 0 °C and the pH of the solution was adjusted to pH 1 with concentrated hydrochloric acid (cooling was maintained throughout the addition). The mixture was evaporated to dryness in vacuo at 30 °C, and the resulting residue was triturated with ethanol (30 mL) at room temperature for 3 h. The precipitated salts were separated by filtration, and the filtrate was concentrated under reduced pressure to an oil, which was crystallized from ethyl acetate to give **34** as a beige powder: yield 370 mg (1.56 mmol, 95%); mp 161–162 °C. Preparative thick-layer chromatography yielded an analytical sample, mp 173–174 °C. Anal. ($C_9H_{12}N_2O_5 \cdot 0.5H_2O$) C, H, N.

Antitumor Studies. The in vitro cytotoxicity against L1210 was evaluated as described previously.[47] L1210 cells were grown in static suspension culture using Fischers medium for leukemic cells of mice, and the growth rate over a 3-day period was determined in the presence of various concentrations of the test compound. The ID_{50} was determined as the concentration required to reduce the growth rate to 50% of the control.

The in vivo antitumor data was furnished by the Division of Cancer Treatment using standard National Cancer Institute Protocols for evaluation of compounds against the mouse leukemias L1210.[48]

Acknowledgment. This research was supported by Research Grant R01-CA-11147 from the National Cancer Institute, National Institutes of Health.

(47) Wotring, L. L.; Townsend, L. B. *Cancer Res.* **1975**, *39*, 3018.
(48) Geran, R. I.; Greenberg, W. H.; MacDonald, M. M.; Shumacher, A. M.; Abbott, B. J. *J. Cancer Chemother. Rep., Part 3* **1972**, *3*, 1.

Synthesis of Some Potential Antihypertensive Phthalazinyl- and Quinoxalinylguanidines

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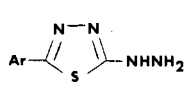
A series of phthalazinyl- and quinoxalinylguanidines has been synthesized and evaluated for potential antihypertensive activity. Unsubstituted guanidines were prepared by treating the appropriate intermediate chloro compounds with guanidine free base. Substituted guanidines were prepared by treating the cyanamides **9** and **16** with the appropriate amine; with hydrazines, cyanamide **9** gave the triazoles **14** and **15**. Moderate falls in blood pressure were observed with compounds **10**, **11**, **14**, and **15**. The triazole **15** caused a 25% fall in heart rate. Some of the compounds (**10**, **11**, **13**, and **18**) displayed weak α-adrenoceptor antagonist properties in vitro, and this activity was confirmed in the pithed rat (in vivo).

2-Aryl-5-hydrazino-1,3,4-thiadiazoles, exemplified by the general structure **1**[1] were designed as analogues of a compound (**2**)[2] known to possess vasodilator activity, the ethylene linkage in **2** being replaced by the bioisosteric "S" atom to give the thiadiazole ring in **1**. The hydrazines **1** were shown to be potent vasodilators,[1] and subsequently it was found that the corresponding thiadiazolylguanidines and aminoimidazolines **3**[3] possessed the same profile of activity, albeit of lower potency.



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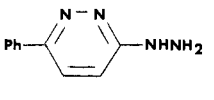

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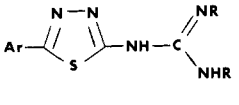

3 R = H or $-(CH_2)_2-$

(1) S. Turner (Reckitt & Colman Ltd.), British Patent Application 25079/76 (1976).
(2) J. Druey and A. Marxer, *J. Med. Pharm. Chem.*, 1, 1 (1959).
(3) M. Myers and S. Turner (Reckitt & Colman Ltd.), unpublished results.

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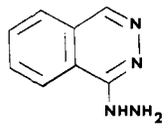
Table I. Effect of Compounds on the Mean Arterial Blood Pressure of Conscious DOCA Hypertensive Rats

compd	*n*	dose, mg/kg po	mean arterial blood pressure, mmHg control	% change 1 h	2 h	3 h	5 h	22 h
saline	15	10 mL	168 ± 3	−6 ± 2	−6 ± 1	−5 ± 1	−2 ± 2	+5 ± 3
10	6	10	162 ± 2	−22 ± 1	−20 ± 2	−24 ± 2	−20 ± 1	+4 ± 3
11	5	10	172 ± 6	−10 ± 2	−10 ± 4	−12 ± 3	−9 ± 2	+8 ± 3
14	4	100	163 ± 3	−14 ± 1	−19 ± 3	−20 ± 5	−23 ± 7	−3 ± 6
15	5	100	168 ± 3	−12 ± 1	−13 ± 1	−12 ± 4	−5 ± 2	+4 ± 1
18	3	10	149 ± 2	−3 ± 3	−5 ± 4	0 ± 1	+5 ± 1	+20 ± 6
hydrallazine	6	10	172 ± 4	−47 ± 1	−45 ± 4	−44 ± 3	−39 ± 3	−15 ± 3
phentolamine	5	20	181 ± 5	−41 ± 3	−34 ± 4	−33 ± 4	−22 ± 3	+6 ± 3

One of the best known peripheral vasodilators is hydrallazine (**4**),[4] and in view of the results obtained with the thiadiazoles **3**, it was decided to examine compounds similar to hydrallazine in which the hydrazine group was replaced by a guanidine or aminoimidazoline moiety.



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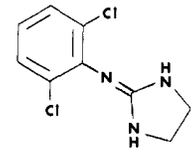

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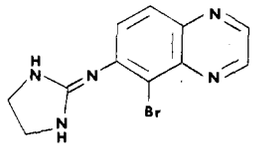
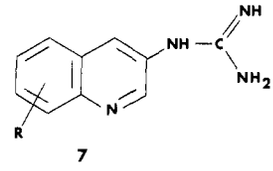
Guanidines and aminoimidazolines based on phthalazine and quinoxaline could also be considered as possible analogues of clonidine (**5**), a centrally acting antihypertensive agent[5] which possesses α-adrenoceptor agonist properties. In particular, a compound, UK 14304 (**6**),[6] has



6 UK 14,304



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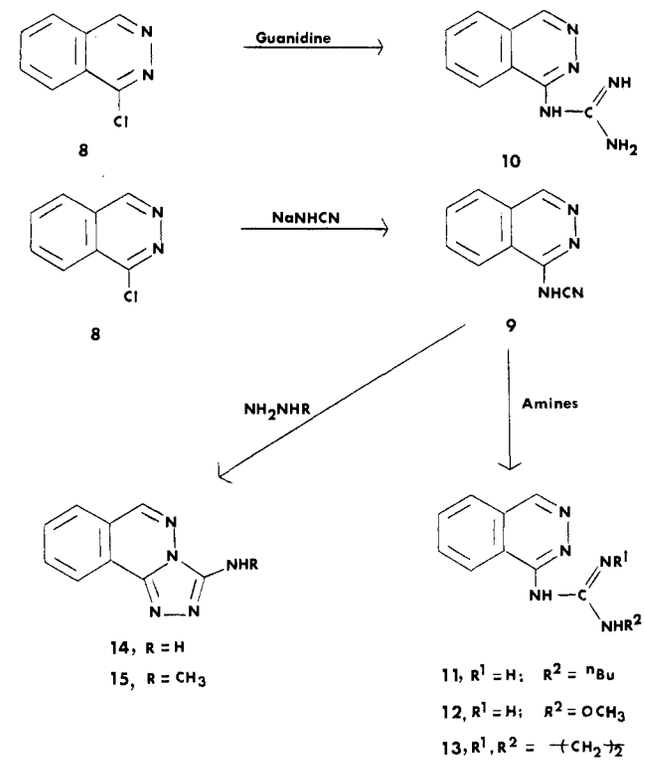
recently been reported to be "clonidine-like", and it is interesting to note that the guanidinoquinolines (**7**) have been claimed as medicaments owing to their strong and long-lasting hypotensive effect.[7] We report here the synthesis and initial screening of some guanidino derivatives of phthalazine and quinoxaline.

Chemistry. The phthalazinylguanidines **10–13** were synthesized by the routes depicted in Scheme I. The unsubstituted guanidine derivative **10** was prepared directly from the reaction of guanidine with the chlorophthalazine **8**. The key intermediate, the cyanamide **9**, for the synthesis of the substituted guanidines **11–13** was readily obtained from 1-chlorophthalazine (**8**) and sodium cyanamide. This intermediate **9** then reacted with the appropriate amine to give the derived products. The reaction of **9** with hydrazines failed to give the required aminoguanidines; these reacted further to give the triazoles **14** and **15**. Proof of the triazole structure **14** came from comparison with an authentic sample[8] prepared by the reaction of cyanogen bromide with hydrallazine (**4**). It

Scheme I



might have been expected that the methyl group in **15** would be attached to one of the two adjacent nitrogen atoms in the triazole ring (i.e., N-2) with a double-bond exocyclic at the 3-position. However, a comparison of the spectroscopic data of **14** and **15** suggests that the structure of **15** is as shown.

The reaction conditions for the preparation of **15** are compatible with a Dimroth[9] type rearrangement occurring with migration of the methyl group from N-2 to the amine group in the 3-position, thus explaining the formation of the structure shown.

The quinoxalinylguanidines **17** and **18** shown in Scheme II were prepared using the same routes as outlined already for the phthalazine compounds.

Results

Retention of vasodilator activity had previously been demonstrated when the hydrazine group in thiadiazolylhydrazines was replaced by a guanidine group.[3] Representative members **10**, **11**, **14**, **15** and **18** of the two series of compounds based, respectively, on the phthalazine and quinoxaline nucleus failed to show any appreciable antihypertensive activity (Table I). At higher dose levels, the compounds **10**, **11**, and **18** produced toxic effects. It is

(4) J. Druey and J. Tripod, *Med. Chem. (Academic)*, **7**, 223 (1967).
(5) P. A. van Zwieten, *Contrib. Nephrol.*, **8**, 200 (1977). P. A. van Zwieten, *J. Pharm. Pharmacol.*, **25**, 89–91 (1973).
(6) H. Ashton and M. D. Rawlins, *Br. J. Clin. Pharmacol.*, **5**, 135 (1978).
(7) Ciba-Geigy, British Patent 889262; *Chem. Abstr.*, **57**, 3420*d* (1962).
(8) K. T. Potts and C. Lovelette, *J. Org. Chem.*, **34**, 3221 (1969); see also Y. Lin, T. L. Fields, and S. A. Lang, *J. Heterocycl. Chem.*, **15**, 311 (1978).
(9) O. Dimroth, *Justus Liebigs Ann. Chem.*, **364**, 183 (1909).

Table II. Effect of Compounds on the Heart Rate of Conscious DOCA Hypertensive Rats

compd[a]	n	dose, mg/kg po	heart rate: mmHg control	heart rate: % change 1 h	2 h	3 h	5 h	22 h
saline	15	10 mL	427 ± 10	+2 ± 3	+2 ± 4	−1 ± 2	−4 ± 3	+2 ± 3
10[b]	6	10	431 ± 11	+2 ± 3	−14 ± 3	+7 ± 3	+1 ± 3	+3 ± 2
11[c]	5	10	365 ± 17	+14 ± 5	+19 ± 5	+21 ± 7	+18 ± 8	+11 ± 7
14	4	100	355 ± 13	+8 ± 5	+7 ± 7	+6 ± 5	+2 ± 3	+7 ± 3
15	5	100	377 ± 13	−23 ± 6	−25 ± 7	−25 ± 7	−25 ± 5	−10 ± 3
18[c]	3	10	358 ± 6	+3 ± 4	−2 ± 1	−5 ± 2	−4 ± 1	+2 ± 1
hydrallazine	6	10	428 ± 16	−5 ± 4	−1 ± 5	+2 ± 5	+11 ± 4	+8 ± 3
phentolamine	5	20	388 ± 14	+21 ± 8	+22 ± 9	+18 ± 9	+11 ± 7	+7 ± 4

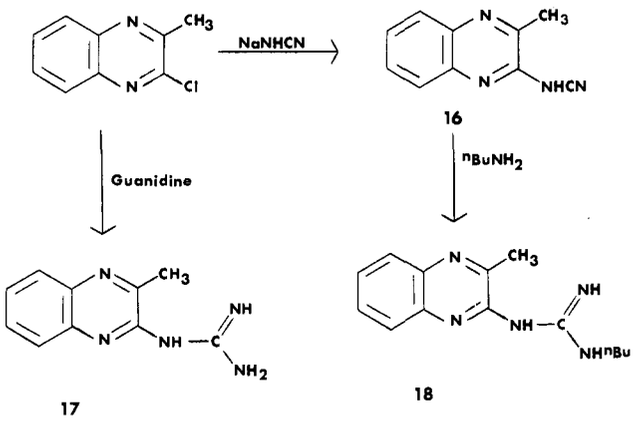
[a] Compounds 12, 13, and 17 were not tested. [b] Toxic at doses of > 50 mg/kg. [c] Toxic at 100 mg/kg.

Table III. α-Adrenoceptor Antagonist Properties

compd[a]	in vitro[b]: presynaptic antagonism pA_2 vs. clonidine (vas deferens)	in vitro[b]: postsynaptic antagonism pA_2 vs. noradrenaline (anococcygeus muscle)	in vivo[c]: threshold intravenous dose, mg/kg, causing reversal of clonidine on: hypogastric nerves	in vivo[c]: blood pressure
10	5.7 ± 0.2	4.9 ± 0.1	3.0	1.0
11	6.6 ± 0.1	5.2 ± 0.1	1.0	1.0
13	6.0 ± 0.2	4.8 ± 0.1	3.0	0.3
18	6.3 ± 0.1	< 5.5 ±	> 1.0	> 1.0
phentolamine	7.9 ± 0.1	7.7 ± 0.1	0.03	0.03

[a] Compounds 9, 12, 14–17 were inactive in the in vitro test situation. [b] Results are the mean of three experiments plus or minus SEM. [c] Results are the mean of five experiments.

Scheme II



interesting to note that the triazole **15** caused a 25% fall in HR (Table II), while the other compounds either showed little change or caused a rise in HR.

The majority of the compounds were also examined for α-adrenoceptor agonist and antagonist properties, and the results are summarized in Table III. Initially, the compounds were tested on isolated tissues for presynaptic (rat vas deferens) and postsynaptic (rat anococcygeus) α-adrenoceptor agonist activity.[10] None of the compounds possessed agonist activity, and consequently, their antagonist properties were assessed. The ability of compounds to antagonize the inhibitory effect of clonidine on the vas deferens and the contractile effect of clonidine on the anococcygeus were used to assess pre- and postsynaptic actions, respectively.[11] Some of the compounds (**10**, **11**, **13**, and **18**) were weak α-adrenoceptor antagonists, and pA_2 values were determined (Table III). This weak antagonism was confirmed in pithed rats.[12] Compounds **9**, **12**, and **14–17** were found to be inactive in the isolated tissue experiments and were therefore not examined in the in vivo test situation.

From the evidence in DOCA rats, none of the compounds had direct vasodilator activity approaching the potency of hydrallazine, although compounds **10** and **14** did possess some activity. Additionally, α-adrenoceptor agonist activity could not be demonstrated, although several compounds displayed weak α-adrenoceptor antagonist activity. However, none approached the potency of phentolamine in either in vitro or in vivo experiments.

Experimental Section

Chemistry. Melting points were determined in a Buchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and MS spectra were recorded on Perkin-Elmer 700, Varian Associates T-60, and LKB-2091 instruments, respectively, and were consistent with the assigned structures. Petrol refers to light petroleum fraction, bp 60–80 °C. Elemental analyses (C, H, and N) for compounds 11–13, **15**, and 17–18 were within 0.4% of the theoretical values. A general description of the synthesis procedure is given where applicable. 1-Chlorophthalazine (**8**) was prepared following the literature method.[13]

Preparation of the Cyanamides. (a) 1-Cyanamidophthalazine (9). A solution of 1-chlorophthalazine (**8**; 5 g, 30.4 mmol) in DMF (30 mL) was added dropwise with stirring to a prepared solution of cyanamide (3.2 g, 76 mmol) and sodium hydride (3.65 g, 50% dispersion in mineral oil, 76 mmol) in dry DMF (125 mL). The reaction mixture was heated to 100 °C under a nitrogen atmosphere for 2 h. The solvent was then removed under vacuum to leave a solid, to which water was added followed by acidification with concentrated HCl to pH 7. The solid was filtered, washed with water, and dried to give the cyanamide **9** (5.1 g, 100%). A small sample was recrystallized from methanol to yield pure **9**: mp 217–219 °C; IR (Nujol) ν_{max} 2180 (m), 1620

(10) J. C. Doxey, *Eur. J. Pharmacol.*, **54**, 185 (1979).
(11) J. C. Doxey, C. F. C. Smith, J. M. Walker, *Br. J. Pharmacol.*, **60**, 91 (1977).
(12) J. Brown, J. C. Doxey, S. Handley, and N. Virdee, "Recent Advances in the Pharmacology of Adrenoceptors", E. Szabadi, C. M. Bradshaw, and P. Bevan, Eds., Elsevier/North Holland Biomedical Press, Amsterdam, 367 (1978).
(13) V. B. Brasyunas and A. S. Podshyunas, *Med. Prom. SSSR*, **13**, 38 (1959); *Chem. Abstr.*, **53**, 16144*f* (1959).

(m), 1610 (s), 1545 (m) cm^{-1}; mass spectrum m/e 170 (M^+), 142 (M - CH_2N), 129 (M - NHCN).

(b) 2-Cyanamido-3-methylquinoxaline (16) was obtained from the reaction of 2-chloro-3-methylquinoxaline (Aldrich Chemical Co.) with sodium cyanamide in 95% yield as a solid: mp 243–245 °C; IR (Nujol) ν_{max} 2190 (m), 1625 (s), 1540 (m) cm^{-1}.

Preparation of Unsubstituted Guanidines. (a) 3-(Phthalazin-1-yl)guanidine Hydrochloride (10). A solution of 1-chlorophthalazine (8; 10 g, 60.8 mmol) in dry dioxane (100 mL) was added to a previously prepared sample of guanidine free base [isolated from guanidine carbonate (12.82 g, 173.3 mmol) and NaOH (5.52 g, 173.3 mmol) in dry methanol (45 mL)]. The reaction mixture was heated at 60 °C for 18 h. The precipitated solid was collected by filtration, washed with water, and dried. The filtrate was evaporated to dryness, and the residues were triturated with acetone to yield more solid. The combined solids were suspended in ether and treated with ethereal HCl to give, after filtration, 10: yield 4.1 g (45%); mp 241–243 °C; IR (Nujol) ν_{max} 1710 (s), 1700 (m), 1620 (m), 1600 (m), 1580 (s), 1538 (m) cm^{-1}; τ (D_2O) 0.17 (1 H, s, H-4), 1.5 (4 H, m, aryl H). Anal. ($C_9H_9N_5 \cdot 2HCl \cdot H_2O$) C, H, N. Recrystallization of 10 from dioxane or methanol resulted in the incorporation of solvent of crystallization.

(b) 3-(3-Methylquinoxalin-2-yl)guanidine hydrochloride (17) was obtained from the reaction of 2-chloro-3-methylquinoxaline with guanidine free base (procedure as in **a** above) in 10% yield (based on recovered starting material) as a solid: mp 290–292 °C (methanol–petrol); IR (Nujol) ν_{max} 3300 (m), 3120 (m), 1690 (s), 1640 (m), 1610 (m), 1580 (m), 1520 (m) cm^{-1}; mass spectrum, m/e 201 (M^+), 186 (M - CH_3), 159 (M - CH_2N_2); τ (D_2O) 2.4–3.1 (4 H, m, aryl H), 8.0 (3 H, s, CH_3). Anal. ($C_{10}H_{11}N_5 \cdot HCl \cdot H_2O$) C, H, N, Cl.

Preparation of Substituted Guanidines. (a) 1-*n*-Butyl-3-(phthalazin-1-yl)guanidine (11). A mixture of 1-cyanamidophthalazine (9; 5 g, 28.8 mmol) and *n*-butylamine (2.85 mL = 2.1 g, 28.8 mmol) was heated at 70 °C for 18 h. The mixture was then partitioned between 2 N sodium hydroxide and ethyl acetate, and the organic layer was collected, washed with water, dried, and evaporated to leave an oil. Chromatography on alumina and elution with 1% ethanol–chloroform gave 2.8 g of crude product. Recrystallization twice from ethyl acetate–petrol gave 11: yield 1.45 g (20%); mp 125–126 °C; IR (Nujol) ν_{max} 3300 (m), 1600 (w), 1540 (s), cm^{-1}; mass spectrum, m/e 243 (M^+), 214 (M - C_2H_5), 200 (M - C_3H_7), 186 (M - C_4H_9), 171 (M - $C_4H_{10}N$); τ ($CDCl_3$) 1.25 (1 H, s, H-4), 1.40 (1 H, m, aryl H), 2.38 (3 H, m, aryl H), 2.6–3.8 (3 H, br s, NH), 6.8 (2 H, t, J = 7 Hz, CH_2), 7.8–9.0 (6 H, m, CH_2), 9.12 (3 H, t, J = 6 Hz, CH_3). Anal. ($C_{13}H_{17}N_5$) C, H, N.

(b) 1-Methoxy-3-(phthalazin-1-yl)guanidine Dihydrochloride (12). A solution of sodium hydroxide (0.52 g, 13 mmol) in methanol (15 mL) was added to a solution of methoxylamine hydrochloride (1.08 g, 13 mmol) in methanol (15 mL). After 0.5 h, the stirred mixture was filtered, and to the filtrate was added the cyanamide 9 (1.0 g, 5.9 mmol). The mixture was heated under reflux for 15 h. Chromatography (after removal of solvent) on alumina and elution with chloroform led to the recovery of cyanamide (9; 0.45 g) and a semisolid, which was dissolved in methanol and treated with ethereal HCl. Collection of the solid gave 12: yield 0.05 g (7%); mp 210–213 °C; IR (Nujol) ν_{max} 1700 (s), 1640 (m), 1560 (s), 1520 (w) cm^{-1}; mass spectrum, m/e 217 (M^+), 186 (M - OCH_3), 171 (M - $NHOCH_3$). Anal. ($C_{10}H_{11}N_5O \cdot 2HCl \cdot H_2O$) C, H, N.

(c) 1-[(4,5-Dihydro-1*H*-imidazol-2-yl)amino]phthalazine Dihydrochloride (13). A mixture of cyanamide 9 (2.95 g, 17.35 mmol) and ethylenediamine (1.27 mL = 1.14 g, 19.08 mmol) was heated at 100 °C for 28 h. Chromatography on alumina and elution with chloroform gave a solid (0.45 g), which was recrystallised from methanol–ethereal HCl to give, 13: yield 0.25 g (7%); mp 235–236 °C; IR (Nujol) ν_{max} 3450 (w), 1640 (s), 1605 (m), 1562 (m) cm^{-1}; mass spectrum, m/e 213 (M^+), 212 (M - 1), 184 (M - C_2H_5) 156 (M - $C_2H_5N_2$); τ (D_2O) 0.15 (1 H, s, H-4), 8.5 (4 H, m, aryl H), 4.04 (4 H, s, CH_2). Anal. ($C_{11}H_{11}N_5 \cdot 2HCl \cdot H_2O$) C, H, N.

(d) 1-*n*-Butyl-3-(3-methylquinoxalin-2-yl)guanidine (18) was isolated from the reaction (18 h at 75 °C) of *n*-butylamine (2.1 g, 28.8 mmol) with cyanamide 16 (4.82 g, 26.2 mmol) in 16% yield as a solid: mp 151–153 °C (ethyl acetate–petrol); IR ν_{max} 1610 (s), 1530 (s) cm^{-1}; mass spectrum m/e 257 (M^+), 242 (M - CH_3), 200 (M - C_4H_9), 185 (M - C_5H_{11}); τ (CD_3OD) 2.2–2.8 (4 H, m, aryl H), 6.64 (2 H, t, J = 7 Hz, CH_2), 7.43 (3 H, s, CH_3), 8.2–8.8 (6 H, m, CH_2), 9.04 (3 H, t, J = 6 Hz, CH_3). Anal. ($C_{14}H_{19}N_5$) C, H, N.

Preparation of Triazoles. (a) 3-(Methylamino)-*s*-triazolo[3,4-*a*]phthalazine (15). A mixture of cyanamide 9 (6 g, 34.56 mmol) and methylhydrazine (1.83 mL = 1.59 g, 34.56 mmol) was heated at 70 °C for 3 h. Dioxane was added to the mixture, and the precipitated solid (4.5 g) was collected, dissolved in ethanol and treated with an excess of ethereal hydrochloric acid. More ether was added to precipitate the salt, which was recrystallized twice from ethanol–ether to give 15: yield 1.2 g (17%); mp 291–294 °C, IR (Nujol) ν_{max} 1670 (s), 1620 (w), 1595 (w), 1570 (m), 1542 (m) cm^{-1}; mass spectrum, m/e 199 (M^+), 156 (M - C_2H_5N) 129 (M - $C_2H_4N_3$); τ (D_2O) 1.27 (1 H, s, H-4), 2.0 (4 H, finely split s, aryl H), 6.05 (3 H, s, CH_3). Anal. ($C_{10}H_8N_5 \cdot HCl$) C, H, N.

(b) 3-Amino-*s*-triazolo[3,4-*a*]phthalazine (14). A sample of 14 (>95% pure) was obtained from the reaction of hydrazine hydrate with cyanamide 9 at 100 °C for 4 h. Proof of the triazole structure 14 came from comparison with an authentic sample[8] prepared from hydrallazine (4): mp 287–291 °C (lit. mp 291 °C); identical by TLC, MS, and IR.

Pharmacology. DOCA Hypertensive Rats. Experiments were carried out on male metacorticoid hypertensive rats.[14] Blood pressure was recorded from an aortic catheter implanted under halothane anesthesia. Experiments were performed not less than 48 h after surgery. Food was removed 18 h before dosing. Blood pressure was measured[15] under conditions of minimal restraint using a Hewlett Packard pressure transducer and twin channel recorder. The blood pressure pulse was used to trigger a tachograph which monitored heart rate. Phentolamine and hydrallazine were used as standards in this test.

Assessment of Presynaptic and Postsynaptic α-Adrenoceptor Agonist and Antagonist Activity in Isolated Tissue Experiments. Increases in the resting tension of the rat anococcygeus muscle and depression of low frequency (0.1 Hz) induced contractions of the rat vas deferens reflected post- and presynaptic agonist properties, respectively.[10]

The pre- and postsynaptic α-adrenoceptor antagonist activity of the compounds was studied using a procedure identical with that used by Doxey et al.[11] Presynaptic α-adrenoceptor antagonist activity was assessed by studying the effects of increasing concentrations of the compounds on cumulative clonidine concentration–response curves on the rat vas deferens stimulated at 0.1 Hz. Postsynaptic α-adrenoceptor antagonist activity was assessed by comparison of control cumulative noradrenaline concentration–response curves with those in the presence of increasing concentrations of the compounds using the rat anococcygeus muscle. Phentolamine was used as a standard in this test.

Assessment of Presynaptic and Postsynaptic α-Adrenoceptor Antagonist Activity in the Pithed Rat. Selective stimulation of hypogastric nerves in the pithed rat leads to a corresponding increase in the tension of the rat vas deferens with little effect on sympathetic discharge to other organs. The presynaptic α-adrenoceptor agonist actions of clonidine inhibit the effects of electrical stimulation on hypogastric nerves. Clonidine also produces a pressor response in pithed rats, an action attributable to its postsynaptic α-adrenoceptor agonist action. The ability of the compounds to reverse the pre- and postsynaptic actions of clonidine (30 μg/kg iv) was compared with that of phentolamine following intravenous injection.[16] A group size of five rats was used for each drug studied.

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(14) H. C. Stanton and J. B. White, *Arch. Int. Pharmacodyn. Ther.*, 154, 351 (1965).
(15) J. R. Weeks and J. A. Jones, *Proc. Soc. Exp. Biol. Med.*, 104, 646 (1960).
(16) J. C. Doxey, J. Everitt, and G. Metcalf, *Eur. J. Pharmacol.*, 51, 1 (1978).