mixture to give 1-methyl-2-(phenylthio)propylamine hydrochloride, mp 138–140 °C. Anal. ($C_{10}H_{16}ClNS$) C, H, N.

1,1-Dimethyl-2-(phenylsulfinyl)ethylamine (58). 1,1-Dimethyl-2-(phenylthio)ethylamine hydrochloride (1.1 g, 0.005 mol) was added in one portion to an ice-cold stirred solution of sodium periodate (1.1 g, 0.005 mol) in aqueous methanol (30 mL, 1:1). The reaction mixture was stirred at ambient temperature for 48 h and filtered. The filtrate was concentrated under reduced pressure and the residue was basified with aqueous NaOH and extracted with chloroform (3 × 50 mL). The chloroform extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was converted into its oxalate salt with ethereal oxalic acid and was crystallized from an EtOAc–EtOH mixture to give 1,1-dimethyl-2-(phenylsulfinyl)ethylamine oxalate: yield 1.2 g (37%); mp 221–223 °C. Anal. [$C_{10}H_{15}NOS\cdot(COOH)_2$] C, H, N.

Using this method there was also prepared 2-(4-chlorophenylsulfinyl)ethylamine hydrochloride (**59**) [mp 157–158.5 °C; yield 53%. Anal. ($C_8H_{10}ClNOS\cdot HCl$) C, H, N] and 2-(4-methylphenylsulfinyl)ethylamine oxalate (**60**) [mp 174–176 °C; yield 70%. Anal. [$C_9H_{13}NOS\cdot(COOH)_2\cdot 0.5H_2O$] C, H, N].

3-(Cyclohexylthio)propylamine (61). A solution of sodium methoxide (prepared from 4.6 g of sodium in 80 mL of methanol) was added dropwise over 60 min to a stirred solution of 3-bromopropylamine hydrobromide (21.9 g, 0.1 mol) and cyclohexanethiol (11.6 g, 0.1 mol) in methanol (80 mL) maintained at −15 °C. The reaction mixture was then stirred at −10 °C for 30 min and allowed to warm to room temperature. Stirring was continued for a further 16 h. The methanol was distilled off and the residue was stirred with ether (200 mL) and filtered. The ether was evaporated off under reduced pressure and the residue was treated with ethereal HCl to give hygroscopic 3-(cyclohexylthio)propylamine hydrochloride, yield 18.3 g (88%).

A sample of the hydrochloride was converted into the free base and treated with ethereal oxalic acid to give the oxalate salt which was crystallized from aqueous MeOH: mp 151–153 °C. Anal. [$C_9H_{19}NS\cdot(COOH)_2$] C, H, N.

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Synthesis and Hypotensive Activity of *N*-Alkyl-*N''*-cyano-*N'*-pyridylguanidines

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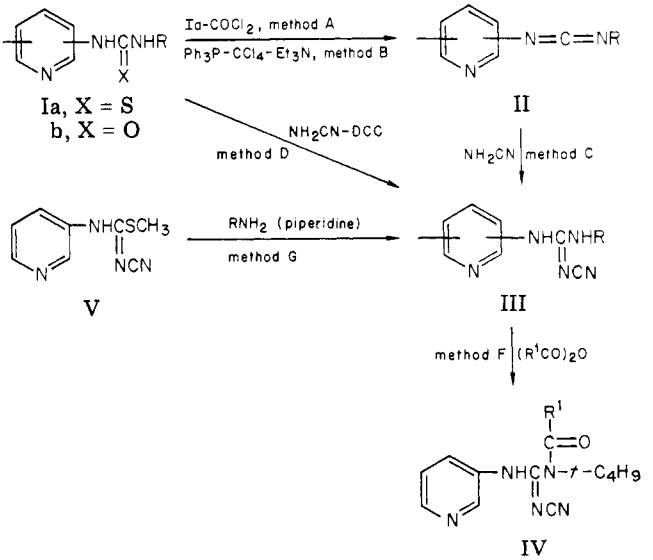
A variety of *N*-alkyl-*N'*-pyridyl-*N''*-cyanoguanidines III was prepared as potential bioisosteres of hypotensive *N*-alkyl-*N'*-pyridylthioureas Ia. Optimal activity of the N,N'-disubstituted cyanoguanidines III was associated with the presence of four to seven carbon branched alkyl and 3- or 4-pyridyl groups. Maximum potency was displayed by *N-tert*-pentyl-*N'*-3-pyridyl-*N''*-cyanoguanidine (**20**). This compound proved to be 200 times more potent than the corresponding thiourea in hypertensive rats and dogs. In comparison with guancydine, which is the de-3-pyridyl analogue of **20**, a 150-fold increase of potency in spontaneously hypertensive rats was obtained with **20** and its *tert*-butyl analogue **19**. The observed activity appears to be due to direct vascular relaxation. On a weight basis compounds **19**, **20**, **50**, and **101** compared favorably with hydralazine.

Several years ago we synthesized a series of *N*-alkyl-*N'*-2-, 3-, and 4-pyridylthioureas[1] Ia (Scheme I) which were found to have pronounced hypotensive activity in rats and dogs.[2] The hypotensive effect of *N-tert*-pentyl-*N'*-3-pyridylthiourea was comparable to that of hydralazine. Urea analogues Ib (Scheme I) were less potent. With the objective of increasing the potency and improving on the therapeutic ratio found with the thioureas, we were led to consider potentially bioisosteric replacements. Our previous finding that the cyanoimino group can function as a biological equivalent of carbonyl oxygen as part of the 6-carboxamide group of penicillins[3] encouraged us to prepare a number of cyanoguanidines[1] III (Scheme I). Meanwhile, a similar approach to molecular modification of gastric antisecretory *N*-imidazolylalkyl-*N'*-alkylthioureas has resulted in a promising cyanoguanidine, cimetidine.[4,5] The appreciation of the structural relation of the title compounds to guancydine, *N*-cyano-*N'*-*tert*-pentylguanidine, drew our attention to an earlier study, evaluating guancydine as the most active antihypertensive compound of a group of monosubstituted *N*-alkyl-*N'*-cyanoguanidines.[6] It was reported that slight structural modification, such as methylation of the unsubstituted amino group, leads to loss of activity. Therefore, it was of interest to assess the activity of the cyanoguanidines III as derivatives of guancydine.

Scheme I



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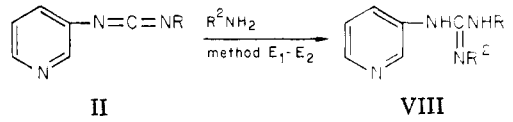
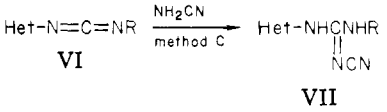
Scheme II



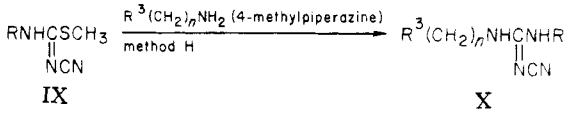
II VIII

Scheme III



VI VII

Scheme IV



IX X

To elucidate the structural requirements for hypotensive activity beyond variation of the alkyl group of III, some related structures were synthesized. These included guanidines, where the cyano group and the pyridine ring were replaced by residues expected to confer similar effects (Schemes II–IV).

Chemistry. A number of 3-pyridylthioureas Ia reacted with phosgene and excess tertiary amine in tetrahydrofuran to afford the carbodiimides II in high yield (method A, Scheme I). This method failed to produce II from Ib. Reaction of Ia,b with triphenylphosphine, carbon tetrachloride, and triethylamine proved to be a more versatile procedure[7] (method B, Scheme I); it was also applicable to the preparation of VI (Scheme III) from the requisite heterocyclic (thio)ureas. With R = *tert*-alkyl addition of cyanamide to neat II or VI brought about a smooth, tertiary amine catalyzed reaction (method C) yielding solid III (Scheme I) and VII (Scheme III). II with R = (iso)alkyl reacted more violently. No II could be isolated from *N*-neopentyl-*N'*-4-pyridylthiourea or *N*-phenyl-*N'*-3- or 4-pyridylthiourea; but here III were obtained in one step by reacting Ia with 2 equiv of cyanamide and dicyclohexylcarbodiimide (DCC) (method D, Scheme I), owing to the inertness of DCC toward cyanamide.[6,8,9]

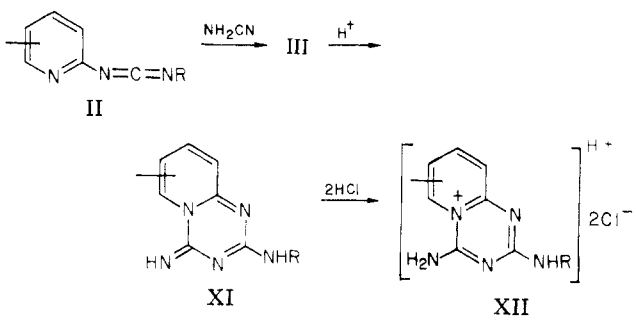
II (R = *tert*-pentyl) furnished VIII with a number of electronegatively substituted amines R^2NH_2 and 1 mol of sodium hydride (method E_1, Scheme II). Reaction of II with hydroxylamine hydrochloride was performed in pyridine (method E_2, Scheme II). VIII ($R^2 = CONH_2$) also resulted from treating III with 0.5 N hydrochloric acid at 50 °C.

Attempts to prepare trisubstituted cyanoguanidines from *N*-cyclopentyl-*N'*-methyl-*N'*-3-pyridylthiourea and from *N,N*-pentamethylene-*N'*-4-pyridylthiourea were unrewarding. III (**19**, Table I), when treated with sodium hydride and acetic or isobutyric anhydride, yielded the monoacyl derivatives IV (method F, Scheme I) whose structures were assigned on the basis of NMR data.

Alternatively, some 3-pyridyl compounds III were obtained by reacting V with excess primary α-unbranched alkylamines in pyridine at room temperature (method G, Scheme I). Cycloalkylamines and piperidine reacted sluggishly and, e.g., isopropyl- and *tert*-butylamine failed to react. More vigorous conditions were required for converting compounds IX into X[5,10,11] (method H, Scheme IV). V and IX were obtained from the respective isothiocyanate, cyanamide, and a tertiary amine and subsequent reaction with methyl iodide.[11]

The cyanoimino structure III was adopted as the most appropriate representation, as it has been shown to be the predominant cyanoguanidine tautomer.[5] III, including **39** (Table I) and IV, displayed amphoteric properties. In addition to the acid solubility conferred by the pyridine group, they were soluble in dilute aqueous alkali—in contrast to guancydine. Under acidic conditions 2-pyridyl compounds III cyclized to XI (Scheme V) which formed stable dihydrochlorides of the tentatively assigned structure XII.

Scheme V



II III XI XII

Pharmacology. Structure–Activity Discussion. Tables I–V describe the hypotensive activity of compounds **1–120** in terms of milligram per kilogram doses which after five daily oral administrations caused a decrease of the blood pressure in spontaneously hypertensive rats of 30 mmHg (MED). Based on this value in relation to the LD_{50}, a rank order was allotted (see Table I). As it is apparent from Table I good activity was generally observed with compounds III having three to seven carbon branched alkyl radicals combined with a 3- or 4-pyridyl group (**8**, **11**, **17–24**, **26**, **50**, **59**, **60**, **65**, and **66**). Similar structural requirements were previously found with thiourea analogues, although at lower potency levels.[2] The poor performance of cycloalkyl derivatives was most clearly shown by comparing **27** with **20**. Also the *N,N*-pentamethylene derivative **39** exhibited low activity. In the 4-pyridyl series the adamantyl group (**67**) was still conferring good hypotensive activity. Apart from 5-bromo substitution (**41**), the presence of substituents on the 3-pyridyl ring caused a marked reduction of activity (**40** and **42–46**). The 2-pyridyl compounds **73–76** as well as their cyclization products XI (Scheme V) possessed only marginal activity.

The most active and less toxic compounds were found among the 3-pyridyl derivatives, e.g., **8**, **17–24**, and **26**. With only one remarkable exception (**50**) the corresponding 4-pyridyl derivatives **47**, **54**, **59–61**, **63**, **65**, and **66** showed lower activity and/or increased toxicity.

The critical importance of the 3-pyridyl group for optimal activity was further stressed by the results obtained with compounds compiled in Tables II and V. Except for **82** and **104**, where insertion of a methylene group still allows for significant retention of activity, replacement of the 3-pyridyl radical gave only weakly active compounds. N-Acetylation of **19** did not influence the hypotensive activity (**101**, Table IV), whereas the introduction of the isobutyryl group caused a 100-fold reduction (**102**, Table IV).

It is noteworthy that the substitution of other polar groups for the CN radical of III invariably resulted in compounds almost devoid of activity (Table III).

Finally, it was of interest to investigate more thoroughly some of the most active compounds (Table VI). For comparison this table includes hydralazine and *N*-*tert*-pentyl-*N'*-3-pyridylthiourea. It appears that the replacement of sulfur by the cyanoimino moiety is resulting in a 200-fold increase of the hypotensive activity in the rat and dog. The increase of the acute toxicity in rats is

limited to approximately 30-fold, thus producing a remarkably improved therapeutic ratio. It may also be noted that single administration of **19** or **20** at the dose of 0.01 mg/kg po in spontaneously hypertensive rats is causing the same fall of the blood pressure as that observed after five daily administrations of 0.1 mg/kg (Table I). This finding suggests the development of tachyphylactic phenomena. This does not occur with the acetyl derivative of **19** (**101**) and with **50**. A distinctive feature of the latter compounds is the prolonged duration of the hypotensive effect. On a milligram basis **101** and **50** are two to ten times more potent than hydralazine, and **19** and **20** are at least 100 times more potent than guancydine (Table VI). The hypotensive effect of **19**, **20**, **50**, and **101** appears to be due primarily to relaxation of peripheral vascular smooth muscles. The contraction of nictitating membranes by preganglionic stimulation was unaffected, and the hypotensive effect was not modified by agents which block α- and β-adrenergic or cholinergic receptors. Decerebration of cats was similarly without effect on the hypotensive activity. In addition, the overall cardiovascular changes associated with produced hypotension in normotensive conscious dogs were characteristic of vasodilator drugs, i.e., increased cardiac output, increased cardiac rate, and decreased total peripheral resistance (Table VII). Similar changes were observed in parallel experiments with hydralazine.

The structural relation of the present compounds to guancydine suggested an investigation of the effect on cardiac noradrenaline in rats. Single or repeated (5 days) administration of **20** (0.1 mg/kg), **19** (0.1 mg/kg), and **50** (1.0 mg/kg) failed to modify cardiac noradrenaline levels, thus suggesting qualitative differences from guancydine.[12] Toxicological studies are now in progress.

Experimental Section

Pharmacology. The approximate oral LD_{50} was determined in mice administered with the different compounds dissolved or suspended in carboxymethylcellulose (0.5%) at four dose levels from 100 to 1000 mg/kg (five mice per dose). For some selected compounds the oral LD_{50} was determined in Sprague–Dawley female rats (body wt = 120–150 g) according to the method of Litchfield and Wilcoxon.[13] In both cases the observation period was 7 days.

The hypotensive activity was determined in spontaneously hypertensive rats (Wistar–Okamoto strain) orally administered with the different compounds dissolved or suspended in carboxymethylcellulose (0.5%) daily, for five consecutive days. The blood pressure was measured in restrained conscious animals by an indirect technique (Gartner cuff connected to an 8000 BP recorder, W+W Electronic, Basel), on the first day of treatment immediately before the administration and then 2, 4, 6, 8, 12, and 24 h later. On the third and fifth day the blood pressure was measured immediately before the administration and then 2, 4, and 8 h later.

The hypotensive activity of some selected compounds was also determined in conscious renal hypertensive dogs. The compounds were administered in soft gelatin capsules. The blood pressure was measured immediately before the administration and then at hourly intervals for 8 h in a semi-insonorized room with the animals in standing position by an indirect technique (Roche Arteriosonde 1010). Cardiac output (CO, L/min) was measured in overnight fasted conscious normotensive dogs by a thermodilution method using an Edwards Labs Model 9500 computer with a Swan-Ganz thermodilution catheter No. 93-118-7 F, permanently inserted in a jugular vein. Mean total peripheral resistance (MTPR) was calculated from the formula MTPR = MABP/CO, where MABP = mean arterial blood pressure (mmHg) (Table VII).

Synthesis. Melting points were uncorrected and recorded with a Tottoli apparatus. Elemental analyses for C, H, N, S, halogen, and H_2O were performed by G. Cornali and W. Egger. Unless stated otherwise analyses were within ±0.4% of the theoretical values. IR spectra were run on a Perkin-Elmer PE 457 spectrometer. Structures III, IV, VII, and X displayed a strong absorption band in the 2160–2180-cm^{-1} region (KBr), attributable to $-C{\equiv}N$. Carbodiimides II and VI had a strong band at 2120–2140 cm^{-1} ($CHCl_3$). NMR data, recorded with a Varian A-60A spectrometer, were consistent with the assigned structures. In compounds III and VII the heterocyclic amino proton signal invariably occurred at lower field as compared with the alkylamino proton. In **19** (Table I) these signals were found at 8.95 and 6.85 ppm [$(CD_3)_2SO$]. In compounds IV and **39** (Table I) the latter signal was absent, thus supporting the proposed structure IV. The preparation and melting points of some hitherto unknown (thio)ureas (Ia,b, Scheme I) have been described.[1] Heterocyclic ureas used as starting materials for **79–85** (Table II) were generally obtained from the requisite carboxylic acids. By standard procedures via the acid chloride and azide they were converted into the isocyanates which, in turn, were reacted with the appropriate alkylamines in benzene solution. In the following experimental details are presented for typical examples of methods A–H.

Method A. *N*-*tert*-Butyl-*N'*-3-pyridylcarbodiimide (II, Scheme I). *N*-*tert*-Butyl-*N'*-3-pyridylthiourea (12.5 g, 60 mmol) was suspended in dry THF (125 mL), and 1.2 M $COCl_2$ in toluene (69 mL) was introduced dropwise, while stirring at 0 °C. After 5 h at 0 °C the mixture was evaporated in vacuo. The residue was treated with THF (100 mL) and *i*-Pr_2EtN (20.4 mL, 120 mmol) at 0 °C, then evaporated, and extracted with three portions of petroleum ether (200 mL). The combined extracts were charcoaled and evaporated to leave the oily carbodiimide in quantitative yield.

Method B. *N*-4-Pyridyl-*N'*-1,2,2-trimethylpropylcarbodiimide (II, Scheme I). A mixture of *N*-4-pyridyl-*N'*-1,2,2-trimethylpropylthiourea (23.7 g, 100 mmol), Ph_3P (34.0 g, 130 mmol), CCl_4 (13.5 mL, 140 mmol), and Et_3N (14 mL, 100 mmol) in CH_2Cl_2 (140 mL) was refluxed for 2 h. After evaporation the residue was triturated with five portions of petroleum ether (150 mL). The combined extracts were reduced to a volume of 150 mL, filtered, and evaporated in vacuo to yield the carbodiimide as an amorphous foam (15.1 g, 74%).

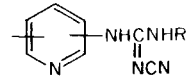
Method C. *N*-*tert*-Butyl-*N''*-cyano-*N'*-3-pyridylguanidine (19, Table I). *N*-*tert*-Butyl-*N'*-3-pyridylcarbodiimide (10.5 g, 60 mmol) was stirred on a water bath at 25 °C. NH_2CN (3.15 g, 75 mmol) and catalytic *i*-Pr_2EtN (0.5 mL) were added. Complete solidification took place over 20 h. The solid was powdered, subsequently treated with petroleum ether and H_2O on a filter, and air-dried: NMR [$(CD_3)_2SO$] (ppm, δ scale) 1.36 (9 H, s), 6.85 (1 H, s), 8.95 (1 H, s), 7.2–7.6 (2 H, m), 8.2–8.5 (2 H, m) (Me_4Si).

Method D. *N''*-Cyano-*N*-phenyl-*N'*-3-pyridylguanidine (37, Table I). *N*-Phenyl-*N'*-3-pyridylthiourea (4.6 g, 20 mmol) was suspended in CH_3CN (20 mL). Dicyclohexylcarbodiimide (DCC) (6.2 g, 30 mmol) and NH_2CN (1.7 g, 40 mmol) were added, followed by catalytic *i*-Pr_2EtN (0.15 mL). After stirring for 6 h at 25 °C the thickening suspension was evaporated in vacuo and left overnight. The residue was stirred with a 1:4 mixture of Et_2O–petroleum ether (150 mL), filtered, and washed with petroleum ether. The filter cake was stirred with 0.8 N aqueous HCl (100 mL) and filtered (Millipore) to remove insoluble *N*,*N'*-dicyclohexylthiourea. From the filtrate the crude product was precipitated by addition of 2 N NaOH (pH 8) while stirring at 0 °C. It was collected by filtration and air-dried: NMR [$(CD_3)_2SO$] (ppm, δ scale) 7.25 (1 H, s), 9.52 (1 H, s), 7.0–7.9 (7 H, m), 8.2–8.6 (2 H, m) (Me_4Si).

***N''*-Cyano-*N*-4-pyridyl-*N'*-1,2,2-trimethylpropylguanidine (50, Table I).** *N*-4-Pyridyl-*N'*-1,2,2-trimethylpropylthiourea (10.7 g, 45 mmol) was suspended in Et_2O (60 mL). NH_2CN (3.8 g, 90 mmol), DCC (18.6 g, 90 mmol), and *i*-Pr_2EtN (0.9 mL) were added. The mixture was stirred for 3 days at 25 °C and evaporated in vacuo. After trituration with two portions of petroleum ether (400 mL) which were decanted, the residue was stirred with H_2O (100 mL) and filtered off. Further workup, adopted from the preceding example, gave the crude compound: NMR [$(CD_3)_2SO$] (ppm, δ scale) 0.92 (9 H, s), 1.12 (3 H, d, J = 6 Hz), 3.97 (1 H, q, J = 6 Hz), 7.28 (1 H, s), 7.44 (1 H, s), 7.12 (2 H, m), 8.37 (2 H, m) (Me_4Si).

Method E_1. *N''*-Carbethoxy-*N*-*tert*-pentyl-*N'*-3-pyridylguanidine (92, Table III). Ethyl carbamate (4.45 g, 50 mmol)

Table I



III

compd	pyridyl	R	mp, °C	method[a]	yield, %[b]	recrystn solvent(s)[c]	formula	LD_{50},[e] mg/kg	MED,[f] mg/kg	rank order[g]
1	3	H	225–226	G	61	A	$C_7H_7N_5$	>1000	50	1
2	3	CH_3	193–194	G	59	A	$C_8H_9N_5$	>1000	>50	0
3	3	*n*-C_3H_7	162–165	G	80	B-C	$C_{10}H_{13}N_5$	>1000	20	2
4	3	*n*-C_4H_9	95–96	C, G	46, 66	B-D	$C_{11}H_{15}N_5$	>1000	20	2
5	3	*n*-C_5H_{11}	131–132	C	55	B-C	$C_{12}H_{17}N_5$	>1000	20	2
6	3	*i*-C_4H_9	146–148	G	83	B-C	$C_{11}H_{15}N_5$	>1000	20	2
7	3	*i*-C_5H_{11}	135–136	G	77	B-D	$C_{12}H_{17}N_5$	>1000	20	2
8	3	*neo*-C_5H_{11}	214–215	C, G	39, 82	E-C	$C_{12}H_{17}N_5$	>1000	2.5	4
9	3	*n*-C_7H_{15}	88–90	G	80	B-C	$C_{14}H_{21}N_5$	>1000	>50	0
10	3	2-ethylhexyl	82–84	G	82	B-C	$C_{15}H_{23}N_5$	>1000	>50	0
11	3	*i*-C_3H_7	154–155	C	49	A	$C_{10}H_{13}N_5$	>1000	2.5	4
12	3	*sec*-C_4H_9	132–135	C	63	B-C	$C_{11}H_{15}N_5$	>1000	20	2
13	3	$CHEt_2$	109–110	C	40	B-C	$C_{12}H_{17}N_5$	600	20	1
14	3	cyclopropyl	170–171	G	86	B-C-D	$C_{10}H_{11}N_5$	>1000	20	2
15	3	cyclopentyl	154–155	G	61	B-C-D	$C_{12}H_{15}N_5$	1000	20	2
16	3	cyclohexyl	184–185	G	59	E-C	$C_{13}H_{17}N_5$	>1000	20	2
17	3	$CH(Me)CMe_3$	167–168	C	63	B-C-D	$C_{13}H_{19}N_5$	1000	1	5
18	3	$CH(i\text{-}C_3H_7)_2$	173–177	C	86	B-C	$C_{14}H_{21}N_5$	>1000	5	4
19	3	*t*-C_4H_9	204–205	C	78	B-C-D	$C_{11}H_{15}N_5$	>1000	0.1	5
20	3	*t*-C_5H_{11}	186–187	C	78	B-C-D	$C_{12}H_{17}N_5$	>1000	0.1	5
21	3	$C(Me_2)(CH_2)_2CH_3$	187–188	C	79	A	$C_{13}H_{19}N_5$	>1000	1	5
22	3	$C(Me_2)CHMe_2$	194–195	C	61	A	$C_{13}H_{19}N_5$	>1000	1	5
23	3	$C(Me)Et_2$	184–186	C	84	A	$C_{13}H_{19}N_5$	>1000	0.5	5
24	3	$C(Me_2)CH_2CHMe_2$	180–181	C	70	B-C-D	$C_{14}H_{21}N_5$	>1000	2.5	4
25	3	$C(Me_2)CMe_3$	193–194	C	80	B-C-D	$C_{14}H_{21}N_5$	>1000	50	1
26	3	CEt_3	192–193	C	73	A	$C_{14}H_{21}N_5$	>1000	1	5
27	3	1-methylcyclobutyl	210–212	C	63	B-C-D	$C_{12}H_{15}N_5$	>1000	50	1
28	3	$C(Me_2)CH_2CMe_3$	180–181	C	83	B-C-D	$C_{15}H_{23}N_5$	>1000	50	1
29	3	1-adamantyl	232–233	C	63	F-C	$C_{17}H_{21}N_5$	>1000	50	1
30	3	$CH_2C(Me)=CH_2$	139–140	G	76	G-D	$C_{11}H_{13}N_5$	1000	20	2
31	3	$(CH_2)_2OEt$	121–122	G	78	B-C-D	$C_{11}H_{15}N_5O$	600	>20	0
32	3	$(CH_2)_2NEt_2$	115–117	G	71	B-C-D	$C_{13}H_{20}N_6$	250	>8	0
33	3	tetrahydrofuryl-2-methyl	128–129	G	67	B-C-D	$C_{12}H_{15}N_5O$	>1000	50	1
34	3	furyl-2-methyl	177–179	G	77	B-C-D	$C_{12}H_{11}N_5O$	>1000	20	2
35	3	benzyl	188–189	G	84	B-D	$C_{14}H_{13}N_5$	>1000	20	2

36	3	β-phenethyl	162–163	G	61	B-C	$C_{15}H_{15}N_5$	>1000	50	1
37	3	phenyl	194–195	D	48	E-C	$C_{13}H_{11}N_5$	>1000	5	3
38	3	2,6-dimethylphenyl	195–200	D	93	A	$C_{15}H_{15}N_5$	>1000	50	1
39	3	RH = pentamethylene	154–155	G	61	B-C-D	$C_{12}H_{15}N_5$	>1000	20	2
40	2-Cl-3	t-C_4H_9	200–202	C	73	B-D	$C_{11}H_{14}ClN_5$	>1000	5	4
41	5-Br-3	t-C_4H_9	152–153	C	63	B-C-D	$C_{11}H_{14}BrN_5$	600	0.5	5
42	6-MeO-3	t-C_4H_9	155–156	C	78	B-C	$C_{12}H_{17}N_5O$	400	15	1
43	2,6-$(MeO)_2$-3	t-C_4H_9	167–168	C	55	B-C-D	$C_{13}H_{19}N_5O_2$	>1000	>50	0
44	2,6-Cl_2-3	t-C_4H_9	191–192	C	73	B-C-D	$C_{11}H_{13}Cl_2N_5$	>1000	>50	0
45	2,4,6-Me_3-3	t-C_4H_9	185–187	H	46	E-C	$C_{14}H_{21}N_5$	>1000	>50	0
46	2,4,6-Me_3-3	t-C_5H_{11}	161–163	H	66	E-C	$C_{15}H_{23}N_5$	800	>25	0
47	4	neo-C_5H_{11}	190–193	D	76	B-C-D	$C_{12}H_{17}N_5$	600	5	3
48	4	$CHEt_2$	195–196	C	77	E	$C_{12}H_{17}N_5$	200	2.5	3
49	4	$CH(Me)CH_2CHMe_2$	177–178	C	52	B-C-D	$C_{13}H_{19}N_5$	1000	35	1
50	4	$CH(Me)CMe_3$	163–164	C, D	69, 67	B-C-D	$C_{13}H_{19}N_5 \cdot H_2O$	600	0.5	5
51	4	$CH(Me)(CH_2)_3CHMe_2$	135–136	C	70	B-C-D	$C_{15}H_{23}N_5$	>1000	50	1
52	4	CH(Me)CH(Me)Et	149–150	C	69	B-C	$C_{13}H_{19}N_5$	250	8	1
53	4	$CH(Et)CHMe_2$	181–182	C	76	B-C-D	$C_{13}H_{19}N_5$	600	5	3
54	4	$CH(i\text{-}C_3H_7)_2$	186–189	C	84	B-C	$C_{14}H_{21}N_5$	250	8	1
55	4	CH(Me)cyclopropyl	183–184	C	55	B-C-D	$C_{12}H_{15}N_5$	200	3	3
56	4	$CH(cyclopropyl)_2$	219–220	D	49	B-C-D	$C_{14}H_{17}N_5$	600	10	2
57	4	cyclohexyl	200–203	D	52	B-C-D	$C_{13}H_{17}N_5$	600	20	1
58	4	cyclooctyl	196–198	C	65	B-C	$C_{15}H_{21}N_5$	600	>20	0
59	4	t-C_4H_9	200–204	C	67	E	$C_{11}H_{15}N_5$	>1000	2.5	4
60	4	t-C_5H_{11}	160–161	C	58	H	$C_{12}H_{17}N_5$	600	2.5	4
61	4	$C(Me_2)CHMe_2$	175–176	C	44	B-C-D	$C_{13}H_{19}N_5$	1000	20	2
62	4	$C(Me_2)CMe_3$	187–190	D	48	B-C-D	$C_{14}H_{21}N_5 \cdot H_2O$	>1000	20	2
63	4	$C(Me_2)CH_2CHMe_2$	153–155	C	63	H	$C_{14}H_{21}N_5$	>1000	20	2
64	4	$C(Me_2)CH_2CMe_3$	195–196	C	60	B-C-D	$C_{15}H_{23}N_5$	>1000	50	1
65	4	$CMeEt_2$	174–175	C	62	B-C-D	$C_{13}H_{19}N_5$	300	0.5	4
66	4	CEt_3	218–220	C	60	E	$C_{14}H_{21}N_5$	>1000	2.5	4
67	4	1-adamantyl	222–223	C	95	B-C-D	$C_{17}H_{21}N_5$	>1000	5	4
68	4	benzyl	170–171	D	51	F-C	$C_{14}H_{13}N_5$	600	5	3
69	4	α-phenethyl	187–188	D	59	B-C-D	$C_{15}H_{15}N_5$	600	10	2
70	4	β-phenethyl	204–207	D	66	B-C-D	$C_{15}H_{15}N_5$	>1000	20	2
71	4	1-phenylisopropyl	181–183	D	43	F-C	$C_{16}H_{17}N_5$	>1000	>50	0
72	4	phenyl	187–188	D	40	F-C	$C_{13}H_{11}N_5$	>1000	50	1
73	2	cyclohexyl	173–174[d]	C	39	G-D	$C_{13}H_{17}N_5$	1000	>35	0
74	2	t-C_4H_9	167–168[d]	C	43	B-C	$C_{11}H_{15}N_5$	600	>20	0
75	5-Cl-2	t-C_4H_9	205–208	C	64	G-D	$C_{11}H_{14}ClN_5$	800	25	1
76	4,6-Me_2-2	t-C_4H_9	201–202	C	76	E-C	$C_{13}H_{19}N_5$	>1000	>50	0

[a] Methods are detailed in the Experimental Section. [b] Based on immediate precursor, after recrystallization. Generally no attempts were made to optimize yields. [c] A, reprecipitation from aqueous HCl–aqueous $NaHCO_3$; B, Me_2CO; C, H_2O; D, petroleum ether; E, EtOH; F, DMF; G, $CHCl_3$; H, dioxane; J, Et_2O; K, benzene; L, n-hexane; M, i-PrOH. [d] With decomposition. [e] Mice, oral administration. Mortality checked 7 days after dosing. [f] Minimal effective dose; daily orally administered dose causing a fall of the blood pressure of 30 mmHg in spontaneously hypertensive rats on the fifth day of administration. [g] 0 = MED > $^1/_{30}$ LD_{50}; 1 = MED ~ $^1/_{30}$ LD_{50}; 2 = MED < $^1/_{30}$ > $^1/_{60}$ LD_{50}; 3 = MED < $^1/_{60}$ > $^1/_{200}$ LD_{50}; 4 = MED < $^1/_{200}$ > $^1/_{1000}$ LD_{50}; 5 = MED ≤ $^1/_{1000}$ LD_{50}.

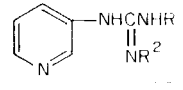
Table II

Het—NHCNHR
‖
NCN
VII

compd	Het	R	mp, °C	method	yield, %	recrystn solvents[c]	formula	LD_{50},[d] mg/kg	MED,[e] mg/kg	rank order[f]
77	*N*-oxido-3-pyridyl	*t*-C_5H_{11}	217–218[a]	*b*	56	E–C	$C_{12}H_{17}N_5O$	>1000	20	2
78	1-methyl-3-pyridinio, iodide	*t*-C_5H_{11}	135–138	*b*	69	E–J	$C_{13}H_{20}IN_5$	>1000	20	2
79	3,5-dimethylisoxazol-4-yl	*t*-C_4H_9	244[a]	C	78	B–C–D	$C_{11}H_{17}N_5O$	>1000	10	3
80	3,5-dimethylisoxazol-4-yl	CH(Me)CMe_3	262–263[a]	C	79	F–C	$C_{13}H_{21}N_5O$	>1000	20	2
81	1-ethyl-3-methylpyrazol-5-yl	*t*-C_4H_9	170–171	C	81	B–C–D	$C_{12}H_{20}N_6$	>1000	10	3
82	1,3,5-trimethylpyrazol-4-yl	*t*-C_4H_9	235–236	C	84	B–C	$C_{12}H_{20}N_6$	>1000	5	4
83	1,3-dimethyl-4-chloropyrazol-5-yl	*t*-C_4H_9	213–214	C	73	B–C–D	$C_{11}H_{17}ClN_6$	>1000	20	2
84	1-methyl-3-*p*-chlorophenylpyrazol-5-yl	*t*-C_4H_9	172–173	C	58	F–C	$C_{16}H_{19}ClN_6$	>1000	>50	0
85	1-methyl-3-*p*-chlorophenylpyrazol-5-yl	*t*-C_5H_{11}	175–176	C	84	F–C	$C_{17}H_{21}ClN_6$	>1000	50	1
86	3-quinolyl	*t*-C_4H_9	228–229	C	74	B–C–D	$C_{15}H_{17}N_5$	>1000	20	2
87	2-methyl-4-quinolyl	*t*-C_5H_{11}	229–230	C	53	F–C	$C_{17}H_{21}N_5$	>1000	10	3

[a] With decomposition. [b] See Experimental Section. [c] See Table I, footnote *c*. [d] See Table I, footnote *e*. [e] See Table I, footnote *f*. [f] See Table I, footnote *g*.

Table III

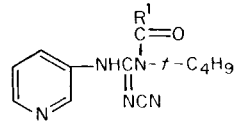


VIII

compd	R^2	R	mp, °C	method	yield, %	recrystn solvent(s)[b]	formula	LD_{50},[c] mg/kg	MED,[d] mg/kg	rank order[e]
88	OH	*t*-C_4H_9	131–132	E_2	44	K	$C_{10}H_{16}N_4O$	1000	>35	0
89	OH	*t*-C_5H_{11}	118–120	E_2	67	K–D	$C_{11}H_{18}N_4O$	600	>20	0
90	OH	$CHEt_2$	139–140	E_2	40	K	$C_{11}H_{18}N_4O$	>1000	50	1
91	OMe	*t*-C_4H_9	83–85	E_2	58	L	$C_{11}H_{18}N_4O$	>1000	50	1
92	COOEt	*t*-C_5H_{11}	71–72	E_1	83	B–C	$C_{14}H_{22}N_4O_2$	600	20	1
93	$CONH_2$	*t*-C_5H_{11}	151–152	E_1	19	B–C	$C_{12}H_{19}N_5O$	>1000	>50	0
94	CHO	*t*-C_5H_{11}	110–111	E_1	43	B–C	$C_{12}H_{18}N_4O$	600	>20	0
95	CF_3CO	*t*-C_5H_{11}	122–123	E_1	73	B–C	$C_{13}H_{17}F_3N_4O$	>1000	>50	0
96	$(n\text{-}C_3H_7)_2NSO_2$	*t*-C_5H_{11}	76–77	E_1	66	B–C	$C_{17}H_{31}N_5O_2S$	>1000	>50	0
97	*p*-$MeC_6H_4SO_2$	*t*-C_5H_{11}	119–120	E_1	51	E–C	$C_{18}H_{24}N_4O_2S$	>1000	>50	0
98	2-thiazolyl	*t*-C_5H_{11}	87–88	E_1	66	A	$C_{14}H_{19}N_5S$	>1000	20	2
99	2-pyrazinyl	*t*-C_5H_{11}	70–72	E_1	67	A	$C_{15}H_{20}N_6$	800	25	1
100	2-pyrimidyl, 2HCl	*t*-C_5H_{11}	206–207[a]	E_1	61	E–J	$C_{15}H_{20}N_6 \cdot 2HCl$	1000	>35	0

[a] With decomposition. [b] See Table I, footnote *c*. [c] See Table I, footnote *e*. [d] See Table I, footnote *f*. [e] See Table I, footnote *g*.

Table IV

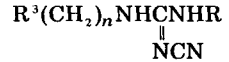


IV

compd	R^1	mp, °C	method	yield, %	recrystn solvents[a]	formula	LD_{50},[b] mg/kg	MED,[c] mg/kg	rank order[d]
101	CH_3, hydrate	84–85	F	53	B-C	$C_{13}H_{17}N_5O \cdot H_2O$	>1000	0.1	5
102	i-C_3H_7	168–170	F	66	B-C	$C_{15}H_{21}N_5O$	>1000	10	3

[a] See Table I, footnote *c*. [b] See Table I, footnote *e*. [c] See Table I, footnote *f*. [d] See Table I, footnote *g*.

Table V



X

compd	R^3	n	R	mp, °C	method	yield, %	recrystn solvent(s)[a]	formula	LD_{50},[b] mg/kg	MED,[c] mg/kg	rank order[d]
103	2-pyridyl	1	t-C_4H_9	156–158	H	82	B-C	$C_{12}H_{17}N_5$	600	>20	0
104	3-pyridyl	1	t-C_4H_9	122–124	H	78	B-C	$C_{12}H_{17}N_5$	>1000	2.5	4
105	4-pyridyl, hydrate	1	t-C_5H_{11}	98–99	H	83	B-C	$C_{13}H_{19}N_5 \cdot H_2O$	>1000	20	2
106	4-pyridyl	1	CH(Me)CMe_3	167–169	H	67	B-C	$C_{14}H_{21}N_5$	>1000	20	2
107	2-pyridyl	2	t-C_4H_9	110–111	C	41	B-C	$C_{13}H_{19}N_5$	800	25	2
108	phenyl	0	t-C_5H_{11}	168–170	H	83	E-C	$C_{13}H_{18}N_4$	>1000	50	1
109	phenyl	0	CH(Me)CMe_3	127–128	C	83	B-C	$C_{14}H_{20}N_4$	>1000	>50	0
110	2,6-dimethylphenyl	0	t-C_4H_9	202–204	H	66	M	$C_{14}H_{20}N_4$	>1000	>50	0
111	2,6-dimethylphenyl	0	t-C_5H_{11}	160–161	H	48	M	$C_{15}H_{22}N_4$	>1000	50	1
112	2,6-dichlorophenyl	0	t-C_4H_9	214–216	C	40	M	$C_{12}H_{14}Cl_2N_4$	>1000	>50	0
113	2-ethoxyphenyl	0	t-C_5H_{11}	94–95	H	66	E-C	$C_{15}H_{22}N_4O$	>1000	20	2
114	4-methoxyphenyl	0	t-C_5H_{11}	146–148	H	64	E-C	$C_{14}H_{20}N_4O$	>1000	50	1
115	4-hydroxyphenyl	0	t-C_4H_9	248–250	H	69	E	$C_{12}H_{16}N_4O$	>1000	>50	0
116	4-dimethylaminophenyl	0	t-C_4H_9	186–187	H	61	E	$C_{14}H_{21}N_5$	>1000	>50	0
117	4-dimethylaminophenyl	0	t-C_5H_{11}	186–187	H	62	E-C	$C_{15}H_{23}N_5$	>1000	>50	0
118	4-acetylaminophenyl	0	t-C_4H_9	240–242	H	33	E	$C_{14}H_{19}N_5O$	>1000	>50	0
119	Me_2N	3	t-C_5H_{11}	113–116	H	71	G-D	$C_{12}H_{25}N_5$	>1000	25	2
120	$R^3(CH_2)_nNH$ = 4-methylpiperazino		t-C_4H_9	137–138	H	75	B-D	$C_{11}H_{21}N_5$	>1000	>50	0
Guan-cydine	H	0	t-C_5H_{11}						800	15	2

[a] See Table I, footnote *c*. [b] See Table I, footnote *e*. [c] See Table I, footnote *f*. [d] See Table I, footnote *g*.

Table VI

compd	LD_{50}, mg/kg po, rat	spontaneously hypertensive rats,[a] mean blood pressure: dose, mg/kg po	initial	max change[c]	duration, h[d]	renal hypertensive dogs,[b] mean blood pressure: dose, mg/kg po	initial	max change[c]	duration, h[d]
N-tert-pentyl-*N'*-3-pyridylthiourea	460 (319-662)	2.5	174 ± 12	−35 ± 11	2	2.5	149 ± 11	−14 ± 6	2
		5.0	176 ± 15	−47 ± 7	2	5.0	153 ± 13	−28 ± 4	2
		10.0	180 ± 13	−69 ± 8	>4	10.0	151 ± 7	−43 ± 8	4
20	14 (8.1-24.5)	0.01	176 ± 14	−27 ± 9	2	0.05	161 ± 15	−41 ± 12	4
		0.05	179 ± 16	−72 ± 15	4	0.1	159 ± 13	−69 ± 14	>6
		0.1	188 ± 18	>−100	4				
19	278 (185-417)	0.01	177 ± 14	−26 ± 11	4	0.05	162 ± 13	−25 ± 11	2
		0.05	173 ± 11	−37 ± 9	6	0.1	157 ± 9	−45 ± 12	4
		0.1	180 ± 13	−72 ± 12	>8	0.25	163 ± 12	−62 ± 14	6
101	615 (402-756)	0.1	181 ± 15	−30 ± 11	4	0.5	149 ± 13	−22	2
		0.25	172 ± 13	−64 ± 13	4	2.0	155 ± 16	−75 ± 12	8
		0.5	178 ± 16	−86 ± 19	>8				
50	570 (392-812)	0.5	196 ± 16	−34 ± 7	8	0.25	156 ± 12	−26 ± 6	4
		1.0	216 ± 13	−68 ± 11	>12	0.50	158 ± 14	−43 ± 9	6
		2.5	191 ± 14	−79 ± 15	>12	1.0	148 ± 12	−67 ± 11	>8
Hydralazine	107 (82-124)	1.0	183 ± 16	−36 ± 13	4	0.5	159 ± 13	−21 ± 7	2
		2.5	208 ± 12	−64 ± 13	>8	1.0	162 ± 14	−42 ± 13	6

[a] Five rats per dose. [b] Three dogs per dose. [c] Measured after single administration. [d] Values of blood pressure 15 mmHg lower than the initial values have been assumed to indicate the persistence of a hypotensive effect.

Table VII. Cardiovascular Changes in Dogs[a]

compd	dose, mg/kg po	blood pressure, mmHg	heart rate, beats/min	cardiac output, L/min	total peripheral resistance, mmHg L^{-1} min
19	0.25	−47 ± 12	+53 ± 16	+2.4 ± 0.9	−25.7 ± 2.7
20	0.10	−38 ± 15	+49 ± 13	+2.6 ± 0.7	−23.4 ± 3.1
50	0.50	−46 ± 13	+59 ± 14	+2.5 ± 0.8	−37.8 ± 4.1
N-tert-pentyl-*N'*-3-pyridylthiourea	5.0	−31 ± 12	+63 ± 19	+1.9 ± 0.4	−21.4 ± 3.7

[a] The values are the mean ± SEM of the maximal changes observed in three to five dogs.

was stirred in dry DMF (40 mL) at 0 °C. NaH (50% mineral oil dispersion) (2.0 g, 40 mmol) was added, followed by *N-tert*-pentyl-*N'*-3-pyridylcarbodiimide (5.7 g, 30 mmol). The mixture was stirred overnight at 8 °C, when it was evaporated exhaustively under high vacuum. After trituration with three portions of petroleum ether (75 mL) the residue was stirred with ice water (125 mL) containing KH_2PO_4 (5.7 g). The resulting solid was filtered, washed with H_2O, and air-dried.

Method E_2. *N-tert*-Butyl-*N''*-hydroxy-*N'*-3-pyridylguanidine (88, Table III). *N-tert*-Butyl-*N'*-3-pyridylcarbodiimide (3.9 g, 22 mmol) was added to a solution of NH_2OH–HCl (1.75 g, 25 mmol) in pyridine (20 mL). After standing overnight at 25 °C H_2O (100 mL) was added and pH was adjusted to 8 by addition of $NaHCO_3$ to cause crystallization of the crude compound, which was filtered and air-dried.

Method F. *N*-Acetyl-*N-tert*-butyl-*N''*-cyano-*N'*-3-pyridylguanidine (101, Table IV). **19** (1.09 g, 5 mmol) was suspended in dry THF (20 mL). While stirring at 0 °C NaH (0.3 g of a 50% oil dispersion, 6 mmol) was introduced, causing precipitation of a sodium salt. Ac_2O (1.25 mL, 12.5 mmol) was added. The thickening suspension was stirred for 2.5 h at 0 °C, then allowed to heat to 25 °C over 4 h and kept overnight at 0 °C. After evaporation in vacuo the residue was extracted with three portions of petroleum ether (30 mL), and ice water (10 mL) was added, adjusting the pH to neutral with 2 N NaOAc. By sustained stirring crystallization of the crude product was slowly induced. It was filtered, washed with H_2O and petroleum ether, and air-dried.

Method G. *N-n*-Butyl-*N''*-cyano-*N'*-3-pyridylguanidine (4, Table I). To *S*-methyl-*N*-cyano-*N'*-3-pyridylisothiourea dihydrate V (Scheme I) (2.30 g, 10 mmol) in pyridine (25 mL) was added *n*-$C_4H_9NH_2$ (10 mL, 100 mmol), and the solution was left at room temperature for 3 days. Pyridine was removed in vacuo and the residue was stirred with H_2O (30 mL), filtered, washed with H_2O, and air-dried: NMR [$(CD_3)_2SO$] (ppm, δ scale) 0.90 (3 H, m), 1.1–1.7 (4 H, m), 2.35 (2 H, m), 7.23 (1 H, t), 8.97 (1 H, s) 7.2–7.8 (2 H, m), 8.2–8.6 (2 H, m) (Me_4Si).

Method H. 1-(*N-tert*-Butyl-*N'*-cyanoguanyl)-4-methylpiperazine (120, Table V). A mixture of *S*-methyl-*N-tert*-butyl-*N'*-cyanoisothiourea IX (Scheme IV) (1.71 g, 10 mmol) and *N*-methylpiperazine (1.20 mL, 11 mmol) in pyridine (10 mL) was refluxed for 4 h. After exhaustive high vacuum evaporation the residue was triturated with *i*-Pr_2O (25 mL), filtered, and washed with *i*-Pr_2O and petroleum ether to leave an almost pure compound.

2-*tert*-Butylamino-4-ammonium-7-chloropyrido[1,2-*a*]-1,3,5-triazinium Dichloride (XII, Scheme V). 75 (3.2 g, 12.5 mmol) was suspended in H_2O (50 mL) and 4 N HCl (6 mL) was added. After stirring for 1 h at 25 °C a clear solution resulted. It was charcoaled and filtered through Celite. The filtrate was made slightly alkaline (pH 8) by adding 2 N NaOH. While stirring at 0 °C the amorphous precipitate gradually turned crystalline, and it was collected by filtration. The semidry material was dissolved in EtOH (30 mL), and 5 N ethereal HCl (10 mL) was introduced while stirring at 0 °C. Addition of Et_2O (200 mL) brought about crystallization of the crude salt which was filtered and washed with Et_2O: mp 216 °C dec. Similarly were prepared XII (unsubstituted pyridyl, R = *tert*-butyl; mp 260–270 °C dec) and XI (unsubstituted pyridyl, R = cyclohexyl, hydrate; mp 83–85 °C).

***N''*-Cyano-*N*-1-oxido-3-pyridyl-*N'-tert*-pentylguanidine (77, Table II). 20** (2.5 g, 11 mmol) was dissolved in glacial AcOH (60 mL), and 30% aqueous H_2O_2 (11.7 mL, 110 mmol) was added with stirring over 5 min. The solution was heated to 60 °C for 4 h. After complete evaporation in vacuo ice water (15 mL) was added, and the crystalline compound was filtered off and washed with H_2O.

***N''*-Cyano-*N*-3-(1-methylpyridinio)-*N'-tert*-pentylguanidine Iodide (78, Table II). 20** (925 mg, 4 mmol) was suspended in $CHCl_3$ (10 mL) and MeI (0.51 mL, 8 mmol) was added. Stirring overnight resulted in a clear solution from which crystalline material gradually deposited. After 6 days at 25 °C the mixture was filtered and washed with $CHCl_3$ (10 mL) and Et_2O to leave an almost pure product.

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References and Notes

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Synthesis and Biological Activity of New 2-Nitroimidazole Derivatives

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In an earlier paper we described the synthesis and the antitrichomonas activity of 2-nitro-α,α,1-trimethyl-1*H*-imidazole-5-methanol (**2**). Starting from this compound, several derivatives have been synthesized. Among these, the phenyl carbonate **8** has been shown to possess activity equal to that of **2** and to be less toxic. This compound therefore is interesting in comparison with some antitrichomonas agents currently in use clinically. Before undertaking an in-depth investigation, compound **8** was subjected to some studies to see whether it has any effects on the central nervous system (CNS). Preliminary results show that, at therapeutic doses, it might induce unwanted CNS effects to a lesser degree than metronidazole.

At the present time, human genital trichomoniasis can be listed among the more important sexually transmitted diseases. However, it is a completely curable and controllable condition. The WHO is collecting data and organizing prevention and treatment centers as part of a worldwide plan for its eradication.[1] For this purpose the nitroimidazoles are the most efficient drugs for systemic treatment. However, there are still some as yet unobtained goals (lowering of dosage, shortening treatment time, getting rid of adverse reactions and cross resistance, etc.) which make it worthwhile to continue research in this field.[2]

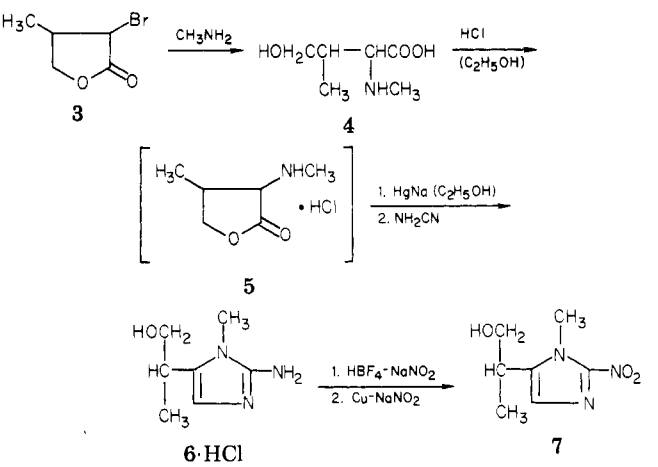
Earlier studies of the metabolism of a 2-nitroimidazole derivative **1** (I, R = H; R′ = CH_3), shown to be particularly active as an oral antitrichomonas agent,[3] led to the isolation[4] of its principal metabolite **2** (I, R = OH; R′ = CH_3) from urines of treated animals. This last compound has been synthesized[5] and shown to possess in vivo activity against *Trichomonas* similar to that of the parent compound, while at the same time it is less toxic.[5]

On the basis of these findings we have undertaken a limited project consisting of (a) synthesis of the isomer **7** (Table I), in which the hydroxyl is moved to the primary carbon; (b) the synthesis of some functional derivatives of **2**; and (c) comparison of **2** with its 5-nitro isomer **14**.

As a result of this program we have found a derivative, **8**, which has activity equal in vivo to that of **2** but is definitely less toxic (Table II) and has a therapeutic index which is even better than those of some antiprotozoan nitroimidazoles in clinical use.

Chemistry. Compound **7** was obtained by the general procedure previously published for the synthesis of 2-nitroimidazoles, outlined in Scheme I. The preparation of the intermediate 2-aminoimidazole **6**, and the transformation of the latter into the corresponding 2-nitroimidazole **7**, proceeded with rather low yields. No attempts were made to improve the yields, since the product showed an activity lower than that of **2**.

Scheme I



The syntheses of some derivatives on the *tert*-hydroxyl group of compound **2** presented some difficulties due to the tendency to dehydrate with formation of the 5-(1-methylethenyl) derivative (I, R, R′ = CH_2).[5] Among different reagents employed, phenyl chloroformate gave the phenyl carbonate **8**, which was also a useful intermediate for the preparation of compounds **9** and **10**. Compound **8** is quite stable in crystalline form and in ethanol or chloroform solution. It led to the hydroxylic starting compound **2** or the methoxy derivative (I, R = OCH_3; R′ = CH_3)[5] by treating it either with water–ethanol or with methanol. Aqueous suspensions of compound **8**, prepared under suitable conditions for use in experimental tests, were stable.

Treatment of **2** with phenyl isocyanate furnished the phenyl carbamate **11**. The benzoate **12** was obtained in low yields, while attempts under various conditions to prepare the acetate led to production of the previously mentioned 5-(1-methylethenyl) derivative.

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