arom), 4.70 (s, 2 H, OH), 6.80 (q, $J = 7$ cps, 1 H, benzylic), 7.8–9.5 [broad envelope, 26 H, $(C_6H_{11}CH_2)_2$]. Further characterization and yield data for the catechols are presented in Table II.

Acknowledgment.—We are pleased to acknowledge the able technical assistance of Mr. Stephen G. Rice, Columbia College, 1967.

Synthesis and Antihypertensive Properties of Some *N*-(Guanidinoalkyl)pyrrolidines

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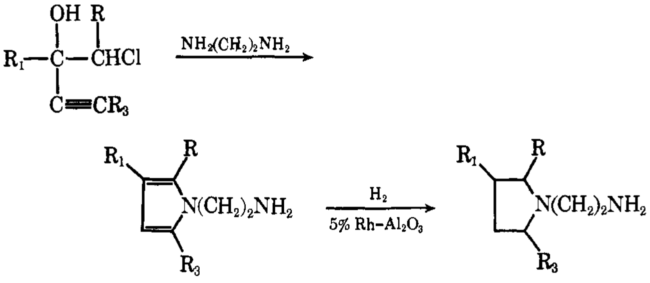
The synthesis of 21 *N*-(guanidinoalkyl)pyrrolidines is described. Some of these, **7a**, **7b**, **10**, **11**, **12**, **12a**, **12b**, **13**, and **21**, exhibited an antihypertensive activity similar to that of guanethidine when tested in renal hypertensive rats. Structure–activity relationships are discussed.

Since the discovery of the antihypertensive action of guanethidine,[1] many related compounds have been synthesized and several have been found to be active antihypertensives[2] which, like guanethidine, mediate their effect *via* adrenergic neurone blockade. This paper describes the preparation and pharmacological properties of a series of *N*-(guanidinoalkyl)pyrrolidines.[3] Details and antihypertensive activities of these compounds are shown in Table I.

Chemistry.—The majority of the compounds listed in Table I were prepared by treating the appropriate *N*-(aminoalkyl)pyrrolidine with *S*-methylpseudothiouronium sulfate in aq EtOH and then neutralizing with 5 *N* H_2SO_4 (method A). Compounds **16–18** were prepared as described in the Experimental Section.

The *N*-(aminoalkyl)pyrrolidine precursors to **1–4**, **7a**, **8**, **9**, **12–14**, and **16–20**, were synthesized as outlined in Schemes I and II. The first step of these syntheses involved the formation of pyrroles from acetylenic carbinols in a manner suggested by the work of Perveev and others.[4,5]

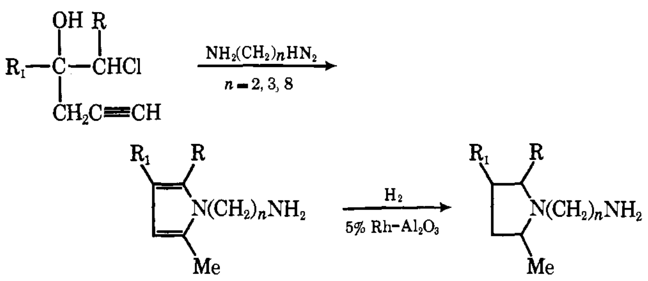
SCHEME I



The precursor to **5** was obtained by catalytic hydrogenation of 1-(2-aminoethyl)-3-phenylpyrrole.

When the pyrrole ring carried substituents on 2 or more C atoms, the catalytic hydrogenation step of Schemes I and II yielded *N*-(aminoalkyl)pyrrolidines as mixtures of stereoisomers. Usually no attempt was made to separate these isomers. In the case of the precursor to **12**, however, the cis and trans isomers of the *N*-(aminoalkyl)pyrrolidine were separated by preparative glpc and converted to the *N*-(guanidinoalkyl)pyrrolidines **12a** and **12b**, respectively. The configurational assignments were made from the pmr spectra on the basis of the mutual shielding effect of Me groups in close proximity. Compound **12a** was also isolated by fractional crystallization of a mixture of the isomeric *N*-(guanidinoalkyl)pyrrolidine sulfate salts.

SCHEME II



In the case of **7a**, the catalytic hydrogenation step of Scheme II gave predominantly the cis isomer of the *N*-(aminoalkyl)pyrrolidine intermediate as shown by glpc. The cis configuration of the Me substituents was confirmed by X-ray crystallographic analysis of the *N*-brosyl derivative.[6] However, synthesis of the *N*-(aminoalkyl)pyrrolidine as outlined in Scheme III, followed by purification as described in the Experimental Section, gave predominantly the trans isomer. Guanylation of this isomer mixture gave **7b**.

The precursor to **21** was obtained from a mixture of isomeric branched-chain compounds.

The precursor to **15** was obtained by catalytic hydrogenation of 2,4-dimethyl-1-(2-methylaminoethyl)pyrrole which was prepared as described in the Experimental Section.

The *N*-(2-aminoethyl)pyrrolidine intermediates for **6**, **10**, and **11** were synthesized as outlined in Scheme IV.

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(1) R. A. Maxwell, A. J. Plummer, F. Schneider, H. Povalski, and A. I. Daniel, *J. Pharmacol. Exp. Ther.*, **128**, 22 (1960).

(2) R. P. Mull and R. A. Maxwell, "Antihypertensive Agents," E. Schlittler, Ed., Academic Press, New York, N. Y., 1967, p 115.

(3) Many of these compds are described by D. Miller and C. S. Fake in British Patent 1,185,080 (1970) and other patents.

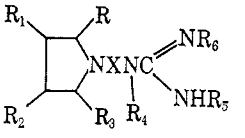
(4) F. Ya. Perveev and E. M. Kuznetsova, *Zh. Obshch. Khim.*, **28**, 2360 (1958); *Chem. Abstr.*, **53**, 3190 (1959).

(5) E. R. Catlin, Ph.D. Thesis, Oxford, England (1964).

(6) Professor G. Sim, University of Sussex, Sussex, England, unpublished work.

TABLE I

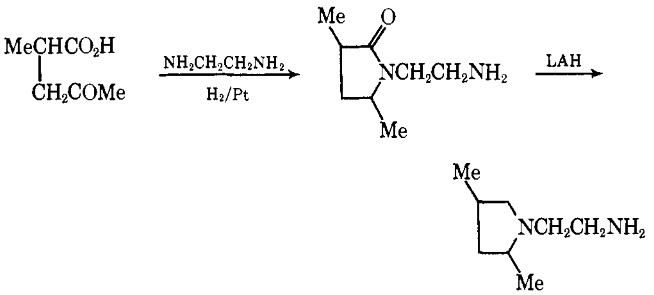
N-(GUANIDINOALKYL)PYRROLIDINES



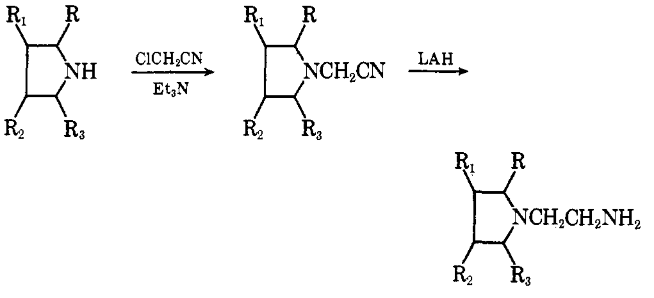
Compd	R	R₁	R₂	R₃	R₄	R₅	R₆	X	Salt	Mp, °C[a,b]	Yield,[c] %	Formula	Analyses	Antihypertensive act.[d] (guanethedine = 1.00) sc	po
1	H	Me	H	H	H	H	H	$(CH_2)_2$	H_2SO_4	243.5–245.5	68	$C_8H_{20}N_4O_4S$	C, H, N, S	0.25	0.41
2	H	Et	H	H	H	H	H	$(CH_2)_2$	H_2SO_4	259–261	74	$C_9H_{22}N_4O_4S$	C, H, S; N[e]	0.38	0.35
3	H	*n*-Pr	H	H	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot 0.5H_2O$	>300	32	$C_{10}H_{24}N_4O_4S\cdot 0.5H_2O$	C, H, N; S[f]	0.21	0.26
4	H	*n*-Bu	H	H	H	H	H	$(CH_2)_2$	H_2SO_4	194–197	73	$C_{11}H_{26}N_4O_4S$	C, H, N, S	0.43	0.16
5	H	Cyclohexyl	H	H	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot 1.5H_2O$	208–211	81	$C_{13}H_{28}N_4O_4S\cdot 1.5H_2O$	C, H, N, S	0.15	0.08
6	H	Ph	H	H	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot 0.5H_2O$	227–237	54	$C_{13}H_{22}N_4O_4S\cdot 0.5H_2O$	C, H, N, S	≪0.10	
7a[g]	H	Me	H	Me	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot H_2O$	291–292	50	$C_9H_{22}N_4O_4S\cdot H_2O$	C, H, N, S	1.50	1.00
7b[h]	H	Me	H	Me	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot H_2O$	292–296	70	$C_9H_{22}N_4O_4S\cdot H_2O$	C, H, N; S[i]	1.70	1.70
8	H	Et	H	Me	H	H	H	$(CH_2)_2$	H_2SO_4	248–250.5	70	$C_{10}H_{24}N_4O_4S$	C, H, N, S	0.21	0.31
9	H	*tert*-Bu	H	Me	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot 0.5H_2O$	246–249	70	$C_{12}H_{28}N_4O_4S\cdot 0.5H_2O$	C, H, N, S	0.11	<0.18
10	Me	H	H	Me	H	H	H	$(CH_2)_2$	H_2SO_4	295–298	65	$C_9H_{22}N_4O_4S$	C, H, N, S	0.81	0.50
11	Me	Me	Me	H	H	H	H	$(CH_2)_2$	H_2SO_4	291–294	66	$C_{10}H_{24}N_4O_4S$	C, H, N; S[j]	1.70	0.60
12[k]	Me	Me	H	H	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot 0.5H_2O$	272–274[l]	86	$C_9H_{22}N_4O_4S\cdot 0.5H_2O$	C, H, N, S	1.60	1.20
12a[m]	Me	Me	H	H	H	H	H	$(CH_2)_2$	H_2SO_4	292–295	48	$C_9H_{22}N_4O_4S$	C, H, N, S	1.00	1.20
12b[n]	Me	Me	H	H	H	H	H	$(CH_2)_2$	$H_2SO_4\cdot 0.5H_2O$	294–295	75	$C_9H_{22}N_4O_4S\cdot 0.5H_2O$	C, H, N, S	1.50	1.20
13	Me	Me	H	Me	H	H	H	$(CH_2)_2$	H_2SO_4	275–278	72	$C_{10}H_{24}N_4O_4S$	C, H, N, S	1.20	1.70
14	H	Me	H	Et	H	H	H	$(CH_2)_2$	H_2SO_4	272–274	71	$C_{10}H_{24}N_4O_4S$	H, N; C, S[o]	0.16	0.35
15	H	Me	H	Me	Me	H	H	$(CH_2)_2$	$H_2SO_4\cdot 1.5H_2O$	254–258	40	$C_{10}H_{24}N_4O_4S\cdot 1.5H_2O$	C, H, N; S[p]	≪0.10	
16	H	Me	H	Me	H	NO_2	H	$(CH_2)_2$	HCl	158[q]	46[r]	$C_9H_{20}ClN_5O_2$	C, H, N, Cl	≪0.10	
17	H	Me	H	Me	H	NH_2	H	$(CH_2)_2$	HI	113–114[s]	67[r]	$C_9H_{22}IN_5$	C, H, N, I	≪0.10	
18	H	Me	H	Me	H	CH_2CH_2		$(CH_2)_2$	$H_2SO_4\cdot H_2O$	219–221[t]	88[r]	$C_{11}H_{24}N_4O_4S\cdot H_2O$	C, H, N, S	≪0.10	
19	H	Me	H	Me	H	H	H	$(CH_2)_3$	$H_2SO_4\cdot 0.5H_2O$	292–294	56	$C_{10}H_{24}N_4O_4S\cdot 0.5H_2O$	C, H, N, S	0.14	0.20
20	H	Me	H	Me	H	H	H	$(CH_2)_8$	$H_2SO_4\cdot H_2O$	*u*	95	$C_{15}H_{34}N_4O_4S\cdot H_2O$	C, H, N, S	≪0.10	
21	H	Me	H	Me	H	H	H	$CHMeCH_2$	$H_2SO_4\cdot 0.5H_2O$	308–309	66	$C_{10}H_{24}N_4O_4S\cdot 0.5H_2O$	C, H, N, S	0.79	0.60

[a] All compds melt with decompn with the exception of **16–18**. [b] Recrystd from EtOH–H_2O unless noted otherwise. [c] Prepd by method A unless noted otherwise. [d] Measured in renal hypertensive rats. Activity is expressed relative to that of guanethidine which is assigned a value of unity. Compds were administered by subcutaneous (sc) and oral (po) routes. [e] N: calcd, 19.85; found, 19.36. [f] S: calcd, 10.50; found, 11.14. [g] A mixt of isomers in which the cis isomer predominates (>90%). [h] A mixt of isomers in which the trans isomer predominates (>82%). [i] S: calcd, 10.67; found, 11.20. [j] S: calcd, 10.81; found, 10.16. [k] Mixt of cis and trans isomers in the ratio 65:35, resp. [l] Not recrystd. [m] Pure cis isomer. [n] Pure trans isomer. [o] C: calcd, 40.56; found, 40.05. S: calcd, 10.81; found, 11.42. [p] S: calcd, 10.19; found 9.41. [q] Recrystd from EtOH. [r] See Experimental Section for method of prepn. [s] Recrystd from EtOH–Et_2O. [t] Recrystd from EtOH–EtOAc. [u] Hygroscopic gum.

SCHEME III



SCHEME IV



Structure–Activity Relationships.—Compounds were tested orally and/or sc for antihypertensive activity in renal hypertensive rats.[7] Doses required to cause a 20% fall in blood pressure were determined and activities were related to the activity of guanethidine. The results shown in Table I indicate that compounds having 2 or more Me substituents on the pyrrolidine ring (*i.e.*, **7a, 7b, 10, 11, 12, 12a, 12b,** and **13**) possess similar antihypertensive activity to guanethidine.

The antihypertensive activity of guanethidine-type compounds is reported[8] to be reduced if smaller rings, such as pyrrolidine, replace the heptamethylenimine ring. We have shown, however, that the presence of 2 or 3 Me substituents on the pyrrolidine ring restores activity whereas the activity declines when larger substituents are present. This indicates that the total number and distribution of C atoms on and in the ring is more important than the ring size.

Compounds having 2 or more substituents at different positions on the pyrrolidine ring exhibit stereoisomerism, but tests on the cis (**7a, 12a**) and trans (**7b, 12b**) isomers of 2 compounds revealed no difference in antihypertensive effect. It would appear, therefore, that the relative stereochemistry of ring substituents is not important for antihypertensive activity.

Other structural requirements for antihypertensive activity agree in general with previous findings for guanethidine analogs. For example, we, like other

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[7] A. Grollman, *Proc. Soc. Exp. Biol. Med.*, **57**, 102 (1944).

[8] R. P. Mull, M. E. Egbert, and M. R. Dapero, *J. Org. Chem.*, **25**, 1953 (1960).

authors,[2,9] observe that maximum activity in guanethidine-type compounds is associated with an ethylene linkage between the heterocyclic N and the guanidine function and that lengthening the C chain causes a decrease in activity. Mull and Maxwell[2] reported that substitution on the ethylene link reduces activity, but we have found that the introduction of a Me substituent as in **21** has little effect on activity. This is in agreement with the observation[10] that the presence of 1 Me substituent on the ethylene link in cyclohexylaminoethylguanidines does not reduce adrenergic neurone blocking potency.

We have also found that substitution on the guanidine function causes loss of activity. It is surprising that **17** and **18** have no detectable effect, since the corresponding aminoguanidine[2,11] and aminoimidazoline[8,12] analogs of guanethidine both possess a guanethidine-like activity with a shorter duration of action.

Pharmacology.—The pharmacology of the di- and trimethyl-substituted *N*-(guanidinoethyl)pyrrolidines (**7a, 10, 11, 12,** and **13**) was investigated in more detail. All were found to be approximately as active as guanethidine as adrenergic neurone blocking agents when tested on the rabbit isolated ear artery preparation.[13] The adrenergic neurone blocking effect of **7a** was further demonstrated on the guinea pig isolated hypogastric nerve–vas deferens preparation,[14,15] the rabbit isolated ileum with sympathetic nerves intact,[16] and the cat superior cervical nerve–nictitating membrane preparation *in vivo*. In each test situation, the potency of **7a** was similar to that of guanethidine. Also, like guanethidine, **7a** potentiated responses to directly acting sympathomimetic amines such as epinephrine and norepinephrine, but inhibited the effects of tyramine, an indirectly acting amine. Compound **7a** had less sympathomimetic activity (*i.e.*, rise in blood pressure, increase in heart rate, and contraction of the nictitating membrane) on iv injection into dogs and cats and less sedative activity in mice (Irwin Profile[17]) then guanethidine. Like guanethidine its adrenergic neurone blocking effect was prevented and/or reversed by desipramine and dexamphetamine. Subject to toxicity clearance, it is proposed to test in clinical practice **7a** as a guanethidine-like antihypertensive.

Experimental Section[18]

Acetylenic Carbinols.—The 3-chloromethylalk-1-yn-3-ols[19] were prepd as described elsewhere. 4-Chloro-3-methylpent-1-yn-3-ol[19] and 4-chloro-3-phenylbut-1-yn-3-ol[20] were prepd in a similar fashion.

Propargyl Carbinols.—4-Chloromethylpent-1-yn-4-ol[21] and 4-chloromethylhex-1-yn-4-ol[21] were prepd by standard procedures.

4-Chloromethyl-5,5-dimethylhex-1-yn-4-ol (22) and 4-*tert*-Butyl-4,5-epoxypent-1-yne (23).—Prop-2-ynylmagnesium bromide was prepd in Et_2O (400 ml) from prop-2-ynyl bromide (71.50 g, 0.60 mole) and Mg turnings (14.65 g, 0.61 g-atom) catalyzed by a crystal of I_2. Once reaction had commenced, the mixt was cooled to −10°. 1-Chloro-3,3-dimethylbutan-2-one (55.66 g, 0.42 mole) in PhH (200 ml) was then added dropwise with stirring during 0.75 hr to the Grignard reagent at −10°. After 4 hr at −10°, the mixt was decompd with 5 *N* H_2SO_4 (250 ml) and H_2O (250 ml). After filtration, the product was extd into Et_2O and the combined exts were washed (H_2O, satd $NaHCO_3$ soln, H_2O) and dried ($MgSO_4$). Fractionation afforded **22** (4.21 g, 6%): mp 65–68° (3.6 mm); $n^{14.5}_{D}$ 1.4828 [*Anal.* ($C_9H_{15}ClO$) H; C: calcd, 61.88; found, 60.14]; and **23** (7.90 g, 14%): bp 36–38.5° (3.5 mm); n^{17}_{D} 1.4482 [*Anal.* ($C_9H_{14}O$) H; C: calcd, 78.26; found, 76.76].

5-Chloro-4-methylhex-1-yn-4-ol (24).—3-Chlorobutan-2-one (210.00 g, 1.97 moles) in PhH (500 ml) was added dropwise to a stirred soln of prop-2-ynylmagnesium bromide, prepd from prop-2-ynyl bromide (357.00 g, 3.00 moles) and Mg turnings (72.00 g, 3.00 g-atoms), in Et_2O (1100 ml) at −10°. The mixt was worked-up in the usual way to give **24** (230.94 g, 80%): bp 35–40° (0.7–1.0 mm); n^{19}_{D} 1.4702. *Anal.* ($C_7H_{11}ClO$) H; C: calcd, 57.35; found, 58.63.

5-Chloromethylhex-3-yn-5-ol (25).—EtMgBr, prepd in Et_2O (700 ml) from EtBr (164.00 g, 1.51 moles) and Mg turnings (36.00 g, 1.50 g-atoms), was converted into but-1-ynylmagnesium bromide by dropwise addn during 1 hr to a satd soln of 1-butyne in Et_2O (700 ml) at 5–10° while a slow stream of 1-butyne was passed continuously through the mixt. Chloroacetone (92.60 g, 1.00 mole) was then added dropwise at 5°. The mixt was stirred for 20 hr at room temp, cooled at 0°, and decompd by addn of satd NH_4Cl soln (250 ml). The inorg salts were filtered off and washed with Et_2O, and the org filtrate was washed (H_2O) and dried ($MgSO_4$). Removal of solvent and fractionation afforded **25** (57.50 g, 39%): bp 81° (11 mm); n^{21}_{D} 1.4710. *Anal.* ($C_7H_{11}ClO$) C, H, Cl.

2-Chloromethylbutan-2-ol (24.03 g, 20%) was also isolated due to reaction between unchanged EtMgBr and chloroacetone.

Substituted 1-(2-Aminoethyl)pyrroles (Table II) (See Schemes I and II).—The chlorocarbinol (1 mole) in EtOH (300 ml) was added dropwise during 1 hr to a refluxing soln of ethylenediamine (6 moles) in EtOH (300 ml), and the mixt was refluxed for 1–5 days. Solvent and excess $(H_2NCH_2)_2$ were removed under vacuum, 40% NaOH soln (1 mole) was added, and H_2O was removed by azeotroping with PhH. After filtration, PhH was removed under vacuum and the crude oil was distd to give the substituted 1-(2-aminoethyl)pyrrole.

Substituted 1-(2-Aminoethyl)pyrrolidines (Table III) (See Schemes I and II).—The 1-(2-aminoethyl)pyrrole (0.1 mole) was hydrogenated at room temp and 35.15 kg/cm² in EtOH (250 ml) and 5 *N* HCl (0.2 mole) in the presence of 5% Rh-Al_2O_3 (5.0 g) catalyst. After 1–3 days, the catalyst was filtered off and the solvent was removed under vacuum. The residue was dissolved in H_2O and the soln was basified with 10% NaOH soln and continuously extd with Et_2O. Removal of Et_2O and distn gave the substituted 1-(2-aminoethyl)pyrrolidine.

Substituted 1-(2-Guanidinoethyl)pyrrolidine Sulfates (1–5, 7a, 8, 9, 12–14). Method A (See Table I).—The 1-(2-aminoethyl)pyrrolidine (0.05 mole) in EtOH (50 ml) was added to a soln of *S*-methylpseudothiouronium sulfate (0.025 mole) in H_2O (25 ml) and the mixt was refluxed for 4 hr while a slow stream of N_2 was passed through to carry away the MeSH formed. After cooling, the soln was neutralized with 5 *N* H_2SO_4 and evapd under vacuum to give a viscous gum which, on boiling with dry EtOH, gave the sulfate salt of the substituted 1-(2-guanidinoethyl)pyrrolidine as colorless microcrystals.

Cis and Trans Isomers of 2,3-Dimethyl-1-(2-guanidinoethyl)-pyrrolidine Sulfate (12a and 12b).—1-(2-Aminoethyl)-2,3-dimethylpyrrolidine (**45**), obtained as a mixt of isomers in the ratio 65:35 (see Table III), was sepd into its 2 component isomers using prep glpc. The samples were injected as a 20% soln in

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[18] Melting points were determined with a Büchi capillary melting point apparatus. Both melting points and boiling points are uncorrected. Ir spectra were obtained with a Perkin-Elmer 137 spectrophotometer. The pmr spectra were recorded on a Varian A-60 spectrometer at 60 MHz (Me_4Si). Where analyses are indicated either in the experiments described herein or in the tables only by symbols of the elements, anal. results obtained for these elements were within ±0.40% of the theoretical values.

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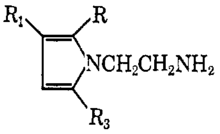
TABLE II

SUBSTITUTED 1-(2-AMINOETHYL)PYRROLES

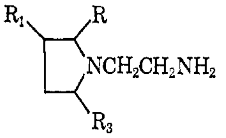


Compd	R	R₁	R₃	Bp (mm), °C	n_D (temp, °C)	Yield, %	Formula	Analyses
26	H	Me	H	65.5–66 (2)	1.5115 (22.5)	47	$C_7H_{12}N_2$	C, H, N
27	H	Et	H	64.5–65 (0.9)	1.5067 (20)	62	$C_8H_{14}N_2$	C, H, N
28	H	*n*-Pr	H	58–60 (0.1)	1.4990 (18.5)	66	$C_9H_{16}N_2$	C, H, N
29	H	*n*-Bu	H	106–107 (3)	1.4982 (21)	49	$C_{10}H_{18}N_2$	C, H, N
30	H	Ph	H	116–122 (0.05)	1.6195 (19)	54	$C_{12}H_{14}N_2$	*a*
31	H	Me	Me	72 (0.9)	1.5140 (17.5)	45	$C_8H_{14}N_2$	C, H, N
32	H	Et	Me	82–87 (1.5)	1.5087 (20)	68	$C_9H_{16}N_2$	C, H, N
33[b]	H	*tert*-Bu	Me	60–62 (0.05)	1.5007 (17)	71	$C_{11}H_{20}N_2$	C, H, N
34	Me	Me	H	72 (0.9)	1.5162 (19)	43	$C_8H_{14}N_2$	C, H, N
35	Me	Me	Me	60–65 (0.01)	1.5171 (21.5)	76	$C_9H_{16}N_2$	H, N; C[c]
36	H	Me	Et	79–80 (0.12)	1.5085 (21.5)	73	$C_9H_{16}N_2$	H, N; C[d]

[a] Characterized as HCl salt, mp 204–207°. *Anal.* ($C_{12}H_{15}ClN_2$) C, H, N, Cl. [b] Also prepd in 72% yield *via* reaction between ethylenediamine and **23** in refluxing EtOH. [c] C: calcd, 71.01; found, 70.28. [d] C: calcd, 71.01; found, 70.43.

TABLE III

SUBSTITUTED 1-(2-AMINOETHYL)PYRROLIDINES



Compd	R	R₁	R₃	Bp (mm), °C	n_D (temp, °C)	Yield, %	Formula	Analyses
37	H	Me	H	66 (14)	1.4631 (16)	68	$C_7H_{16}N_2$	C, H, N
38	H	Et	H	79–81 (14)	1.4633 (18.5)	57	$C_8H_{18}N_2$	C, H, N
39	H	*n*-Pr	H	59.5–60 (0.7)	1.4641 (17.5)	74	$C_9H_{20}N_2$	C, H; N[a]
40	H	*n*-Bu	H	90–92 (1)	1.4650 (20)	62	$C_{10}H_{22}N_2$	
41[b]	H	Cyclohexyl	H	90–91 (0.4)	1.4938 (18)	41	$C_{12}H_{24}N_2$	C, H; N[c]
42[d,e]	H	Me	Me	71 (14)	1.4578 (17)	48	$C_8H_{18}N_2$	C, N; H[f]
43	H	Et	Me	88–89.5 (15)	1.4598 (16.5)	36	$C_9H_{20}N_2$	*g*
44	H	*tert*-Bu	Me	105–109 (14)	1.4618 (21)	60	$C_{11}H_{24}N_2$	H, N; C[h]
45[i,e]	Me	Me	H	81–83 (18)	1.4640 (20)	56.5	$C_8H_{18}N_2$	H, N; C[j]
46	Me	Me	Me	78.5–80 (11)	1.4995 (20)	77	$C_9H_{20}N_2$	*k*
47	H	Me	Et	82 (12)	1.4610 (21)	88	$C_9H_{20}N_2$	*l*

[a] N: calcd, 17.93; found, 16.86. [b] Obtd *via* catalytic hydrogenation of **30**. [c] N: calcd, 14.27; found, 13.85. [d] Obtd as a mixt of cis and trans isomers in the ratio 90:10, resp, as shown by glpc. [e] Glpc was carried out on a column of silicone-treated Celite which had been treated with 5% w/w KOH and 15% w/w Ucon. The column temp was programmed from 53 to 150° at 0.5°/min. [f] H: calcd, 12.75; found, 13.19. [g] Characterized as di-*p*-toluenesulfonate salt, mp 157–158°. *Anal.* ($C_{23}H_{36}N_2O_6S_2$) H, N, S; C: calcd, 55.20; found, 54.41. [h] C: calcd, 71.68; found, 69.97. [i] Obtained as mixt of cis and trans isomers in the ratio 65:35 as shown by glpc. [j] C: calcd, 67.55; found, 66.95. [k] Characterized as dipicrate, mp 227–228° dec. *Anal.* ($C_{21}H_{26}N_8O_{14}$) C, H, N. [l] Characterized as dipicrate, mp 180–181° dec. *Anal.* ($C_{21}H_{26}N_8O_{14}$) C, H, N.

nonane on to a 3.3 m × 9.275 mm Al column packed with 20% w/w silicone oil DC 550 on Chromosorb W (80–100 mesh) using N_2 as carrier gas. The column temp was programmed from 73 to 173° at 0.5°/min, and a flame ionization detector was used. The isomers both absorbed traces of H_2O during collection and storage. The pmr spectrum (D_2O + DCl) of the minor isomer (shorter retention time) exhibited 2 doublets (J = 6.5 Hz) at δ 1.12 and 1.45 (CH_3 of trans Me substituents); whereas the pmr spectrum (D_2O + DCl) of the major isomer showed two doublets (J = 7 Hz) at δ 1.02 and 1.27 (CH_3 of cis Me substituents). Guanylation of these isomeric amines *via* method A gave **12b** as the sulfate hemihydrate (75%), mp 294–295° dec [*Anal.* ($C_9H_{22}N_4O_4S \cdot 0.5H_2O$) C, H, N, S], and **12a** as the sulfate (48%), mp 292–295° (decomp) [*Anal.* ($C_9H_{22}N_4O_4S$) C, H, N, S].

The sulfate salt **12a** was also obtained by fractional crystn from EtOH-H_2O of the 65:35 mixt of isomers described in Table I.

1-(3-Aminopropyl)-2,4-dimethylpyrrole (48).—4-Chloromethylpent-1-yn-4-ol (25.00 g, 0.19 mole) was added dropwise to a refluxing soln of 1,3-diaminopropane (84.50 g, 1.14 moles) in EtOH (200 ml), and the mixt was refluxed for 24 hr. Solvent was removed under vacuum, 40% NaOH soln (19.00 ml, 0.19 mole) was added, and the mixt was extd with $CHCl_3$. The combined exts were concd to small bulk under vacuum and the concd soln was then extd with pet ether (60–80°). The pet ether exts were dried ($MgSO_4$) and evapd under vacuum, and the crude oil (17.06 g) was distd to give **48** (14.10 g, 49%): bp 78–80° (1.0 mm); $n^{20}D$ 1.5081. *Anal.* ($C_9H_{16}N_2$) H, N; C: calcd, 71.01; found, 71.55.

1-(8-Amino-1-octyl)-2,4-dimethylpyrrole (49).—4-Chloromethylpent-1-yn-4-ol (17.20 g, 0.13 mole) was added dropwise to a refluxing soln of 1,8-diaminooctane (60.00 g, 0.42 mole) in EtOH (150 ml), and the mixt was refluxed for 24 hr. Work-up as described in the preceding expt gave **49** (17.20 g, 60%): bp 112–114° (0.02 mm); $n^{20}D$ 1.4919. *Anal.* ($C_{14}H_{26}N_2$) C, H, N.

2,4-Dimethyl-1-(2-hydroxyethyl)pyrrole (50).—4-Chloromethylpent-1-yn-4-ol (132.50 g, 1 mole) was added dropwise to a refluxing soln of ethanolamine (366.00 g, 6 moles) in EtOH (200 ml) and the mixt was refluxed for 24 hr. Solvent and excess ethanolamine were removed under vacuum, 40% NaOH soln (100 ml, 1 mole) was added, and H_2O was removed by azeotroping with PhH. After filtration, PhH was removed under vacuum, and the crude oil was fractionated to give **50** (68.60 g, 50%): bp 76–78° (0.4 mm); $n^{20}D$ 1.5094 [lit.[4] bp 83–85° (1 mm); $n^{20}D$ 1.5067]. *Anal.* ($C_8H_{13}NO$) C, H, N.

2-(2,4-Dimethyl-1-pyrrolyl)ethyl *p*-Toluenesulfonate (51).—TsCl (30.00 g, 0.158 mole) was added to a soln of **50** (20.00 g, 0.144 mole) in pyridine (100 ml) at 0°. After 4 days at 0°, the mixt was poured into ice water (400 g) with vigorous stirring to give a grey ppt of **51** (32.74 g, 77%), mp 93–94°. *Anal.* ($C_{15}H_{19}NO_3S$) H, N, S; C: calcd, 61.45; found, 60.82.

2,4-Dimethyl-1-(2-methylaminoethyl)pyrrole (52).—**51** (28.24 g, 0.0965 mole) was added portionwise to 33% alcoholic $MeNH_2$ soln (210 ml, 2.24 moles) and the mixt was allowed to stand at room temp for 7 days. Solvent and excess $MeNH_2$ were removed under vacuum, 40% NaOH soln (10 ml, 0.1 mole) was added, and the soln was extd thoroughly with Et_2O. After drying ($MgSO_4$), the combined Et_2O exts were evapd under vacuum and the crude oil was distd to give **52** (6.68 g, 46%): bp 67–69° (1 mm); $n^{20}\mathrm{D}$ 1.4995, characterized as the picrate, mp 158°. *Anal.* ($C_{15}H_{19}N_5O_7$) C, H, N.

1-(3-Aminopropyl)-2,4-dimethylpyrrolidine (53), 1-(8-Amino-1-octyl)-2,4-dimethylpyrrolidine (54), and 2,4-Dimethyl-1-(2-methylaminoethyl)pyrrolidine (55).—The pyrroles (**48**, **49**, and **52**) were hydrogenated at room temp and 35.15 kg/cm² in EtOH and 5 *N* HCl with 5% Rh–Al_2O_3 as catalyst. The hydrogenation mixts were worked-up in the usual way to give the aminoalkylpyrrolidines: **53** (66%), bp 82–86° (13 mm), $n^{21}\mathrm{D}$ 1.4595, characterized as the dipicrate, mp 195–198° dec [*Anal.* ($C_{21}H_{26}N_8O_{14}$) C, H, N]; **54** (50%), bp 96° (0.35 mm), $n^{23}\mathrm{D}$ 1.4620 [*Anal.* ($C_{14}H_{30}N_2$) H, N; C: calcd, 74.27; found, 73.84; and **55** (66%), bp 89–90° (25 mm), $n^{21}\mathrm{D}$ 1.4490, characterized as the dipicrate, mp 141–142° dec [*Anal.* ($C_{21}H_{26}N_8O_{14}$) C, H, N].

2,4-Dimethyl-1-(3-guanidinopropyl)pyrrolidine Sulfate (19), 2,4-Dimethyl-1-(8-guanidino-1-octyl)pyrrolidine Sulfate (20), and *N*-2-(2,4-Dimethyl-1-pyrrolidinyl)ethyl-*N*-methylguanidine Sulfate (15).—The amines (**53**, **54**, and **55**) were guanylated *via* method A to give the sulfate salts of the guanidines (see Table I).

Mixture of 1-(2-Aminopropyl)-2,4-dimethylpyrrole (56) and 2-(2,4-Dimethyl-1-pyrrolyl)propylamine (57).—4-Chloromethylpent-1-yn-4-ol (50.00 g, 0.377 mole) was added dropwise to a refluxing soln of 1,2-diaminopropane (165.00 g, 2.23 moles) in EtOH (100 ml) and the mixt was refluxed for 19 hr. Solvent and excess diamine were removed under vacuum, 40% NaOH soln (38 ml, 0.38 mole) was added, and H_2O was removed by azeotroping with PhH. After filtration, PhH was removed under vacuum and the crude product was distd to give a colorless oil (26.88 g, 47%), bp 60–65° (0.05 mm). This product was shown by pmr and glpc to be a mixt of **56** and **57** in the ratio 65:35, resp [isomer mixt, *Anal.* ($C_9H_{16}N_2$) H, N; C: calcd, 71.01; found 69.75]. This mixt of pyrroles was fractionated through a stainless steel spinning-band column. Clean sepn was not achieved, but an enriched fraction (6.65 g), contg **56** and **57** in the ratio 78:22, resp, was obtained.

1-(2-Aminopropyl)-2,4-dimethylpyrrolidine (58) and 2-(2,4-Dimethyl-1-pyrrolidinyl)propylamine (59).—The foregoing enriched fraction (6.60 g) contg **56** and **57** in the ratio 78:22, resp, was hydrogenated at room temp and atmospheric pressure in EtOH and 5 *N* HCl, with 5% Rh–Al_2O_3 catalyst. After 24 hr, the mixt was worked-up in the usual way to give a colorless oil (5.50 g, 81%), bp 81–82° (17 mm), shown by glpc to be a mixt of **58** and **59** in the ratio 78:22, resp [isomer mixt, *Anal.* ($C_9H_{20}N_2$) C, H, N]. This mixt of pyrrolidines was sepd by short-column chromatog on silica gel G (elution with 4:1 EtOH–5 *N* NH_4OH) to give **58** (0.83 g) and **59** (0.28 g). Compd **58** was the component with the highest R_f value. Both **58** and **59** were obtained as mixts of stereoisomers as indicated by glpc.

2-(2,4-Dimethyl-1-pyrrolidinyl)propylguanidine Sulfate (21).—The amine **59** (0.20 g) was guanylated *via* method A to give **21** as the sulfate hemihydrate (0.26 g, 66%). See Table I.

Attempted Guanylation of 58.—The amine **58** was subjected to guanylation *via* method A but, although the evolution of MeSH was apparent, a pure sample of the desired guanidine sulfate could not be isolated.

***N*-2-(2,4-Dimethyl-1-pyrrolidinyl)ethyl-*N*¹-nitroguanidine and Hydrochloride (16).**—To a stirred soln of **42** (14.20 g, 0.1 mole) in 1:1 EtOH–H_2O (100 ml), *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (10.11 g, 0.07 mole) was added portionwise over 10 min, keeping the temp of the mixt below 20°. After stirring overnight, the cryst product was filtered off and recrystd (EtOAc) to give the substituted nitroguanidine (7.45 g, 46%), mp 121°. *Anal.* ($C_9H_{19}N_5O_2$) C, H, N.

The nitroguanidine (6.90 g) was dissolved in EtCOMe and a stream of anhyd HCl was passed through the soln causing the pptn of **16** (7.95 g, 99%), mp 158°. See Table I.

***N*-Amino-*N*′-2-(2,4-dimethyl-1-pyrrolidinyl)ethylguanidine Hydriodide (17).**—A soln of **42** (7.10 g, 0.05 mole) in EtOH (10 ml) was added dropwise to a soln of *S*-methylpseudothiosemicarbazide·HI (8.20 g, 0.035 mole) in EtOH (30 ml) at room temp. The mixt was kept at room temp for 30 hr and was then evapd to dryness under vacuum. The viscous oily residue was crystd from EtOH–Et_2O to give **17** as colorless plates (7.75 g, 67%), mp 113–114°. See Table I.

2,4-Dimethyl-1-(2-imidazol-2′-in-2′-ylaminoethyl)pyrrolidine and Sulfate (18).—An intimate mixt of **42** (21.86 g, 0.154 mole) and 2-nitroamino-2-imidazoline (4.41 g, 0.034 mole) was heated up to 130° in an Vigreux flask. The initial vigorous reaction was allowed to moderate and the contents of the flask were then heated up to 200° and maintained at this temp for 10 min. After cooling, the mixt was fractionated to give the substituted 2-amino-2-imidazoline (6.35 g, 88%), bp 147–149° (0.01 mm), as a colorless oil which solidified on standing to give hygroscopic crystals, mp 72–73°, characterized as the sulfate hydrate (**18**), mp 219–221°. See Table I.

3-Phenylpyrrolidine (60).—Phenylsuccinic acid (mp 161–165°; lit.[22] mp 162–165°) was prepd as described by Miller and Long[22] and was converted to phenylsuccinimide (mp 74–77°; lit.[23] mp 90°) by the method of Wegscheider and Hecht.[23] The succinimide was then reduced with LAH and worked-up in the usual way to give **60** (38%): bp 70–71° (0.7 mm); $n^{23}\mathrm{D}$ 1.5528 [lit.[24] bp 92–94° (2 mm); $n^{20}\mathrm{D}$ 1.5545].

2,3,4-Trimethylpyrrolidine (61).—3-Carbethoxy-4-methylpyrrole-2-carboxylic acid (mp 198–200°; lit.[25] mp 195.7–196.8°) was prepd as described by Lancaster and VanderWerf[25] and was reduced with LAH to give 2,3,4-trimethylpyrrole [bp 79–81° (15 mm), mp 37–39°; lit.[26] bp 79° (15 mm), mp 39.5–40°] as described by Hinman and Theodoropulos.[26]

The trimethylpyrrole (10.00 g, 0.92 mole) was then hydrogenated in glacial AcOH (200 ml) at room temp and atmospheric pressure, in the presence of 5% Rh–Al_2O_3 catalyst (4 g). After 12 days, the catalyst was filtered off and AcOH was removed under vacuum. The residue was dissolved in H_2O and the soln was basified with 40% NaOH soln and continuously extd with Et_2O. Removal of Et_2O and distn gave **61** (4.01 g, 39%): bp 31–34° (12 mm); $n^{22}\mathrm{D}$ 1.4380.

1-Cyanomethyl-2,5-dimethylpyrrolidine (62), 1-Cyanomethyl-2,3,4-trimethylpyrrolidine (63), and 1-Cyanomethyl-3-phenylpyrrolidine (64) (See Scheme IV).—2,5-Dimethylpyrrolidine (19.80 g, 0.2 mole) was dissolved in PhH (20 ml) contg Et_3N (20.20 g, 0.2 mole). Chloroacetonitrile (15.10 g, 0.2 mole) was added to the stirred soln and stirring was continued for 24 hr. The resulting ppt of $Et_3N \cdot HCl$ was filtered off, PhH was removed under vacuum, and the residual oil was distd to give **62** (16.43 g, 60%): bp 82° (12 mm); $n^{21}\mathrm{D}$ 1.4502. *Anal.* ($C_8H_{14}N_2$) C, H, N.

Similarly, **61** was converted to **63** (60%), bp 110° (22 mm), $n^{21}\mathrm{D}$ 1.4538 [*Anal.* ($C_9H_{16}N_2$) H, N; C: calcd, 71.01; found, 70.35], and **60** was converted to **64** (63%), bp 130° (0.25 mm), mp 40–41° [*Anal.* ($C_{12}H_{14}N_2$) C, H, N].

1-(2-Aminoethyl)-2,5-dimethylpyrrolidine (65), 1-(2-Aminoethyl-2,3,4-trimethylpyrrolidine (66), and 1-(2-Aminoethyl)-3-phenylpyrrolidine (67) (See Scheme IV).—A soln of **62** (6.90 g, 0.05 mole) in Et_2O (50 ml) was added dropwise to a stirred suspension of LAH (2.85 g, 0.075 mole) in Et_2O (50 ml) under N_2. At the end of the addn, the mixt was refluxed for 3 hr, allowed to cool, and H_2O (2.85 ml), 15% NaOH soln (2.85 ml), and H_2O (8.55 ml) were added. After filtration, the soln was dried ($MgSO_4$), Et_2O was removed under vacuum, and the crude oil was distd to give **65** (2.25 g, 32%): bp 65–66° (10 mm); $n^{20.5}\mathrm{D}$ 1.4615.

Similarly, **63** was reduced to **66** (30%), bp 85–86° (14 mm), and **64** was reduced to **67** (67%), bp 106–108° (0.8 mm), $n^{20}\mathrm{D}$ 1.5412.

2,5-Dimethyl-1-(2-guanidinoethyl)pyrrolidine Sulfate (10), 1-(2-Guanidinoethyl)-2,3,4-trimethylpyrrolidine Sulfate (11), and 1-(2-Guanidinoethyl)-3-phenylpyrrolidine Sulfate (6).—The

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amines (**65**, **66**, and **67**) were guanylated *via* method A to give the sulfate salts of the guanidines (see Table I).

***N*-2-(2,4-Dimethyl-1-pyrrolidinyl)ethyl-*p*-bromobenzenesulfonamide (68) and *N*-2-(2,4-Dimethyl-1-pyrrolidinyl)ethyl-*p*-iodobenzenesulfonamide (69).**—A mixt of **42** (6.70, 0.047 mole; see Table III), brosyl chloride (18.00 g, 0.070 mole), and 10% NaOH soln (150 ml) was stirred vigorously for 24 hr at 20°. The soln was then warmed to 100° for 15 min, cooled, and washed with Et_2O. The aq phase was then adjusted to pH 9 by addn of 5 *N* HCl and extd thoroughly with Et_2O. The combined Et_2O exts were dried ($MgSO_4$) and evapd to dryness to give a yellow oil (7.57 g, 45%), which solidified on standing to give colorless crystals, mp 56–60°. Recrystn from 60–80° pet ether gave the *N*-brosyl deriv **68** as colorless rods, mp 64.5–66°. *Anal.* ($C_{14}H_{21}BrN_2O_2S$) C, H, N, Br, S.

Similarly, the *N*-iodosyl deriv **69** was obtained as colorless prisms, mp 82–83°. *Anal.* ($C_{14}H_{21}IN_2O_2S$) C, H, N, I, S.

α-Methyllevulinic Acid (70) (See Scheme III).—2-Methylpent-4-ynoic acid [bp 100–104° (11 mm), $n^{20}D$ 1.4439; lit.[27] bp 109° (20 mm), $n^{20}D$ 1.4435] was prepared by the method of Colonge and Gelin.[27] The pentynoic acid (78.40 g, 0.70 mole) was then hydrated by treatment with a 5% soln of $HgSO_4$ in 10% H_2SO_4 (700 ml) at 100° for 1 hr. After cooling, the soln was extd thoroughly with Et_2O, the exts were dried ($MgSO_4$) and evapd under vacuum, and distn afforded **70** (61.60 g, 68%): bp 106–114° (0.7 mm); $n^{22}D$ 1.4398 [lit.[28] bp 103° (1 mm); $n^{19}D$ 1.4388].

1-(2-Aminoethyl)-2,4-dimethyl-5-pyrrolidone (71) (See Scheme III).—A suspension of Adams catalyst (1.0 g) in EtOH (100 ml) was hydrogenated to Pt. A soln of **70** (26.00 g, 0.20 mole) and ethylenediamine (72.00 g, 1.20 moles) in EtOH (200 ml) was then added and the mixt was hydrogenated at atmospheric pressure and room temp. After 24 hr the theoretical vol of H_2 had been absorbed and the mixt was filtered through kieselguhr to remove catalyst. EtOH and excess ethylenediamine were removed under vacuum and the residual oil was dissolved in 5 *N* HCl. The acidic soln was washed with $CHCl_3$, basified with 40% NaOH soln, and extd thoroughly with $CHCl_3$. After drying ($MgSO_4$), the exts were evapd under vacuum and distn gave **71** (24.00 g, 77%): bp 94–98° (0.4 mm); $n^{19.5}D$ 1.4861. *Anal.* ($C_8H_{16}N_2O$) H, N; C: calcd, 61.51; found, 61.04.

Mainly Trans Isomer of 1-(2-Aminoethyl)-2,4-dimethylpyrrolidine (42) (See Scheme III).—A soln of **71** (7.80 g, 0.05 mole) in Et_2O (60 ml) was added dropwise to a stirred suspension of LAH (5.70 g, 0.15 mole) in Et_2O (60 ml) in 0.5 hr. The mixt was refluxed overnight and worked up in the usual way to give a colorless oil (5.59 g), bp 70–71° (11 mm), shown by glpc to be a mixt of **42** (90%, cis and trans isomers present in the ratio 51:39, resp) and an unidentified product (10%). Fractional distn of this mixt through a stainless steel spinning-band column afforded a fraction (0.85 g) contg **42** (91%, cis and trans isomers present in the ratio 22:69, resp) and the unidentified product (9%) as shown by glpc. This fraction was treated with excess picric acid in EtOH to give bright yellow crystals, mp 199–204°. Repeated recrystn from H_2O gave the purified dipicrate, mp 204–209°. *Anal.* ($C_{20}H_{24}N_8O_{14}$) C, H, N. The dipicrate was treated with 10% NaOH soln and the soln was satd with NaCl. The resulting inorg ppt was filtered off, the filtrate was extd thoroughly with Et_2O, and the exts were dried (K_2CO_3) and evapd under vacuum to give **42** as a colorless oil (0.42 g). This purified product was shown by glpc to be a mixt of cis and trans isomers in the ratio 18:82, resp.

Mainly Trans Isomer of 2,4-Dimethyl-1-(2-guanidinoethyl)-pyrrolidine Sulfate (7b).—**42** (0.32 g, a mixt of cis and trans isomers in the ratio 18:82, resp) was guanylated *via* method A to give **7b** as the sulfate hydrate (0.47 g, 70%), mp 292–296° dec). *Anal.* ($C_9H_{22}N_4O_4S \cdot H_2O$) C, H, N; S: calcd, 10.67; found, 11.20.

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