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,<sup>1</sup> many related compounds have been synthesized and several have been found to be active antihypertensives<sup>2</sup> 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.<sup>3</sup> 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<sub>2</sub>SO<sub>4</sub> (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.<sup>4,5</sup>

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

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



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.

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.<sup>6</sup> 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.

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

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

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

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

<sup>(6)</sup> Professor G. Sim, University of Sussex, Sussex, England, unpublished work.

TABLE I N-(GUANIDINOALKYL)PYRROLIDINES



											Vield	c		Antihyper act. <sup>d</sup> (gua	tensive anethe-
Compd	R	R1	R,	B.	R₄	R۵	Re	x	Salt	Mp. °C <sup>a,b</sup>	77 77	, Formula	Analyses	sc	1.007
1	ъ	Ma	и. U	υ	u	ц.	u	(CH-)-	H.SO.	243 5-	69	C.H.N.O.S	CHNS	0.25	0 41
1	11	Me	11	n	11	11	11	$(C112)_2$	112504	245 5	00	081120114040	0, 11, 11, 5	0.20	0.41
2	н	Et	н	н	н	н	н	$(CH_2)_2$	H <sub>2</sub> SO <sub>4</sub>	259-261	74	C2H22N4O4S	C. H. S: N <sup>e</sup>	0.38	0.35
3	н	n-Pr	н	н	н	н	н	$(CH_2)_2$	H <sub>2</sub> SO <sub>4</sub> 0.5H <sub>2</sub> O	>300	32	C10H24N4O4S 0.5H2O	C. H. N: S <sup>f</sup>	0.21	0.26
4	H	n-Bu	н	н	H	н	н	(CH <sub>2</sub> ) <sub>2</sub>	H <sub>2</sub> SO <sub>4</sub>	194-197	73	C11H26N4O4S	C. H. N. S	0.43	0.16
5	н	Cvelo-	Н	н	H	H	н	$(CH_2)_2$	$H_2SO_4 \cdot 1.5H_2O$	208-211	81	$C_{13}H_{28}N_4O_4S \cdot 1.5H_2O$	C, H, N, S	0.15	0.08
-		hexvl													
6	н	Ph	н	н	н	H	$\mathbf{H}$	$(CH_{2})_{2}$	$H_2SO_4 \cdot 0.5H_2O$	227-237	54	$C_{13}H_{22}N_4O_4S \cdot 0.5H_2O$	C, H, N, S	$\ll 0.10$	
7a <sup>g</sup>	н	Me	н	Me	н	н	н	$(CH_2)_2$	$H_2SO_4$ $H_2O$	291 - 292	50	C <sub>9</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub> S · H <sub>2</sub> O	C, H, N, S	1.50	1.00
$7b^{h}$	н	Me	н	Me	н	н	$\mathbf{H}$	$(CH_2)_2$	$H_2SO_4 \cdot H_2O$	292 - 296	70	$C_{9}H_{22}N_{4}O_{4}S \cdot H_{2}O$	C, H, N; S <sup>i</sup>	1.70	1.70
8	н	$\mathbf{Et}$	н	Me	н	Н	н	$(CH_{2})_{2}$	H <sub>2</sub> SO <sub>4</sub>	248-250.5	70	C10H24N4O4S	C, H, N, S	0.21	0.31
9	н	tert-Bu	н	Me	н	н	н	$(CH_2)_2$	$H_2SO_4 \cdot 0.5H_2O$	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	н	н	н	$(CH_{2})_{2}$	$H_2SO_4$	295 - 298	65	C <sub>9</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub> S	C, H, N, S	0.81	0.50
11	Me	Me	Me	н	н	H	$\mathbf{H}$	$(CH_{2})_{2}$	$H_2SO_4$	291 - 294	66	$C_{10}H_{24}N_4O_4S$	C, H, N; S <sup><math>i</math></sup>	1.70	0.60
$12^k$	Me	Me	н	н	н	н	н	$(CH_{2})_{2}$	$H_2SO_4 \cdot 0.5H_2O$	$272 - 274^{l}$	86	$C_9H_{22}N_4O_4S\cdot 0.5H_2O$	C, H, N, S	1.60	1,20
$12a^m$	Me	Me	н	н	Η	н	н	$(CH_{2})_{2}$	$H_2SO_4$	292 - 295	48	C <sub>9</sub> H <sub>22</sub> N <sub>4</sub> O <sub>4</sub> S	C, H, N, S	1.00	1.20
$12b^n$	Me	Me	н	$\mathbf{H}$	н	$\mathbf{H}$	н	$(CH_{2})_{2}$	$H_2SO_4 \cdot 0.5H_2O$	294 - 295	75	$C_9H_{22}N_4O_4S \cdot 0.5H_2O$	C, H, N, S	1.50	1.20
13	Мe	Me	н	Me	н	н	н	$(CH_2)_2$	$H_2SO_4$	275 - 278	72	$C_{10}H_{24}N_4O_4S$	C, H, N, S	1.20	1.70
14	Н	Me	н	$\mathbf{E}\mathbf{t}$	H	н	H	$(CH_2)_2$	$H_2SO_4$	272 - 274	71	$C_{10}H_{24}N_4O_4S$	H, N; C, S <sup>o</sup>	0.16	0.35
15	н	Me	н	Me	Me	н	н	$(CH_2)_2$	$H_2SO_4 \cdot 1.5H_2O$	254 - 258	40	$C_{10}H_{24}N_4O_4S \cdot 1.5H_2O$	C, H, N; S <sup>p</sup>	≪0.10	
16	н	Me	н	Me	н	$NO_2$	Н	$(CH_2)_2$	HCl	$158^q$	$46^r$	$C_9H_{20}ClN_5O_2$	C, H, N, Cl	≪0.10	
17	н	Me	Н	Me	н	$\rm NH_2$	н	$(CH_2)_2$	HI	$113 - 114^{8}$	$67^{r}$	$C_9H_{22}IN_5$	С, Н, Ň, І	≪0.10	
18	Н	Me	н	Me	н	CH <sub>2</sub> C	$2H_2$	$(CH_{2})_{2}$	$H_2SO_4 \cdot H_2O$	$219-221^{t}$	88 <sup>r</sup>	$C_{11}H_{24}N_4O_4S \cdot H_2O$	С, Н, N, S	$\ll 0.10$	
19	н	Me	н	Me	н	н	н	$(CH_2)_3$	$H_2SO_4 \cdot 0.5H_2O$	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	Η	Me	Η	н	Н	(CH <sub>2</sub> ) <sub>8</sub>	$H_2SO_4 \cdot H_2O$	u	95	$C_{15}H_{34}N_4O_4S\cdot H_2O$	C, H, N, S	≪0.10	
21	Η	Me	н	Me	н	н	н	$CHMeCH_2$	$H_2SO_4 \cdot 0.5H_2O$	308-309	66	$C_{10}H_{24}N_4O_4S \cdot 0.5H_2O$	C, H, N, S	0.79	0.60

<sup>a</sup> All compds melt with decompn with the exception of **16-18**. <sup>b</sup> Recrystd from EtOH-H<sub>2</sub>O unless noted otherwise. <sup>c</sup> Prepd by method A unless noted otherwise. <sup>d</sup> 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. <sup>e</sup> N: calcd, 19.85; found, 19.36. <sup>f</sup> S: calcd, 10.50; found, 11.14. <sup>g</sup> A mixt of isomers in which the cis isomer predominates (>90%). <sup>h</sup> A mixt of isomers in which the trans isomer predominates (>82%). <sup>i</sup> S: calcd, 10.67; found, 11.20. <sup>j</sup> S: calcd, 10.81; found, 10.16. <sup>k</sup> Mixt of cis and trans isomers in the ratio 65:35, resp. <sup>l</sup> Not recrystd. <sup>m</sup> Pure cis isomer. <sup>n</sup> Pure trans isomer. <sup>o</sup> C: calcd, 40.56; found, 40.05. S: calcd, 10.81; found, 11.42. <sup>p</sup>S: calcd, 10.19; found 9.41. <sup>q</sup> Recrystd from EtOH. <sup>r</sup> See Experimental Section for method of prepn. <sup>e</sup> Recrystd from EtOH-Et<sub>2</sub>O. <sup>t</sup> Recrystd from EtOH-EtOAc. <sup>w</sup> Hygroscopic gum.



Structure-Activity Relationships.—Compounds were tested orally and/or sc for antihypertensive activity in renal hypertensive rats.<sup>7</sup> 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<sup>8</sup> 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

<sup>(8)</sup> R. P. Mull, M. E. Egbert, and M. R. Dapero, J. Org. Chem., 25, 1953 (1960).

authors,<sup>2,9</sup> 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<sup>2</sup> 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<sup>10</sup> 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<sup>2,11</sup> and aminoimidazoline<sup>8,12</sup> 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.<sup>13</sup> The adrenergic neurone blocking effect of **7a** was further demonstrated on the guinea pig isolated hypogastric nerve-vas deferens preparation,<sup>14,15</sup> the rabbit isolated ileum with sympathetic nerves intact,<sup>16</sup> 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<sup>17</sup>) 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<sup>18</sup>

Acetylenic Carbinols.—The 3-chloromethylalk-1-yn-3-ols<sup>19</sup> were prepd as described elsewhere. 4-Chloro-3-methylpent-1-

(9) E. Schlittler, J. Druey, and A. Marxer, Fortsch. Arzneimittelforsch., 4, 341 (1962).

(10) M. J. Rand and J. Wilson, Eur. J. Pharmacol., 1, 200 (1967).

(11) H. Najer, R. Giudicelli, and J. Sette, Bull. Soc. Chim. Fr., 559 (1962).

(12) H. Najer, R. Giudicelli, and J. Sette, *ibid.*, 556 (1962).

(13) I. S. De La Lande and M. J. Rand, Aust. J. Exp. Biol. Med. Sci., 43, 639 (1965).

(14) S. Hukovic, Brit. J. Pharmacol. Chemother., 16, 188 (1961).

(15) A. T. Birmingham and A. B. Wilson, ibid., 21, 569 (1963).

(16) B. Finkleman, J. Physiol. (London), 70, 145 (1930).

(17) S. Irwin, Psychopharmacologia, 13, 222 (1968).

(18) Melting points were determined with a Buchi 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 (MetSi). 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  $\pm 0.40\%$  of the theoretical values.

(19) (a) E. R. H. Jones, L. Skatteböl, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956); (b) E. R. H. Jones, British Patent 836,280 (1960); (c) M. D. Mehta and E. R. Catlin, British Patent 877,497 (1961).

yn-3-ol<sup>19</sup> and 4-chloro-3-phenylbut-1-yn-3-ol<sup>20</sup> were prepd in a similar fashion.

**Propargyl Carbinols.**—4-Chloromethylpent-1-yn-4-ol<sup>21</sup> and 4-chloromethylhex-1-yn-4-ol<sup>21</sup> 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<sub>2</sub>O (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<sub>2</sub>. 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<sub>2</sub>SO<sub>4</sub> (250 ml) and H<sub>2</sub>O (250 ml). After filtration, the product was extd into Et<sub>2</sub>O and the combined exts were washed (H<sub>2</sub>O, satd NaHCO<sub>3</sub> soln, H<sub>2</sub>O) and dried (MgSO<sub>4</sub>). Fractionation afforded **22** (4.21 g, 6%): mp 65-68° (3.6 mm); n<sup>14.5</sup>D 1.4828 [Anal. (C<sub>9</sub>H<sub>15</sub>Cl) H; C: calcd, 61.88; found, 60.14]; and **23** (7.90 g, 14%): bp 36-38.5° (3.5 mm); n<sup>17</sup>D 1.4482 [Anal. (C<sub>9</sub>H<sub>14</sub>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<sub>2</sub>O (1100 ml) at  $-10^{\circ}$ . The mixt was worked up in the usual way to give 24 (230.94 g, 80%): bp 35-40° (0.7-1.0 mm);  $n^{19}$  1.4702. Anal. (C<sub>7</sub>H<sub>n</sub>ClO) H; C: calcd, 57.35; found, 58.63.

5-Chloromethylhex-3-yn-5-ol (25).—EtMgBr, prepd in Et<sub>2</sub>O (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<sub>2</sub>O (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<sub>4</sub>Cl soln (250 ml). The inorg salts were filtered off and washed with Et<sub>2</sub>O, and the org filtrate was washed (H<sub>2</sub>O) and dried (MgSO<sub>4</sub>). Removal of solvent and fractionation afforded **25** (57.50 g, 39%): bp 81° (11 mm);  $n^{21}$ D 1.4710. Anal. (C<sub>7</sub>-H<sub>11</sub>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/cm<sup>2</sup> in EtOH (250 ml) and 5 N HCl (0.2 mole) in the presence of 5% Rh-Al<sub>2</sub>O<sub>3</sub> (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<sub>2</sub>O and the soln was basified with 10% NaOH soln and continuously extd with Et<sub>2</sub>O. Removal of Et<sub>2</sub>O 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<sub>2</sub>O (25 ml) and the mixt was refluxed for 4 hr while a slow stream of N<sub>2</sub> was passed through to carry away the MeSH formed. After cooling, the soln was neutralized with 5 N H<sub>2</sub>SO<sub>4</sub> 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

<sup>(20)</sup> D. Miller, J. Chem. Soc. C, 12 (1969).

<sup>(21)</sup> H. Gutmann, O. Isler, G. Ryser, P. Zeller, and B. Pellmont, Helv. Chim. Acta, 42, 719 (1959).

TABLE II SUBSTITUTED 1-(2-AMINOETHYL)PYRROLES



<sup>a</sup> Characterized as HCl salt, mp 204-207°. Anal. (C12H15ClN2) C, H, N, Cl. <sup>b</sup> Also prepd in 72% yield via reaction between ethylenediamine and 23 in refluxing EtOH. C: calcd, 71.01; found, 70.28. C: calcd, 71.01; found, 70.43.

TABLE III SUBSTITUTED 1-(2-AMINOETHYL)PYRROLIDINES .R

 $R_1$ 

				NCH <sub>2</sub>	$CH_2NH_2$			
				R <sub>3</sub>				
Compd	R	$\mathbf{R}_1$	R۵	Bp (mm), °C	nD (temp, °C)	Yield, %	Formula	Analyses
37	н	${ m Me}$	$\mathbf{H}$	<b>66</b> (14)	1.4631(16)	68	$\mathrm{C_7H_{16}N_2}$	С, Н, N
38	H	$\mathbf{Et}$	Н	79-81 (14)	1.4633(18.5)	57	$\mathrm{C_8H_{18}N_2}$	C, H, N
39	H	n-Pr	Н	59.5-60 (0.7)	1.4641 (17.5)	74	$C_9H_{20}N_2$	C, H; $N^{a}$
40	н	n-Bu	H	90-92(1)	1.4650(20)	62	$C_{19}H_{22}N_2$	
$41^{b}$	н	Cyclo-	Η	90-91(0.4)	1.4938(18)	41	$C_{12}H_{24}N_2$	C, H; $N^c$
		hexyl						
$42^{d,e}$	$\mathbf{H}$	Me	${ m Me}$	71 (14)	1.4578(17)	48	$\mathrm{C_8H_{18}N_2}$	C, N; $H^{f}$
43	н	$\mathbf{Et}$	${ m Me}$	88-89.5 (15)	1.4598(16.5)	36	$\mathrm{C}_{9}\mathrm{H}_{20}\mathrm{N}_{2}$	g
44	H	<i>tert-</i> Bu	Me	105-109(14)	1.4618 (21)	60	$C_{11}H_{24}N_2$	H, N; $C^h$
$45^{i,e}$	Me	${ m Me}$	H	81-83 (18)	1.4640(20)	56.5	$C_8H_{18}N_2$	H, N; $C^{i}$
46	${\bf Me}$	${ m Me}$	Me	78.5 - 80(11)	1.4995(20)	77	$\mathrm{C}_{9}\mathrm{H}_{20}\mathrm{N}_{2}$	k
47	$\mathbf{H}$	${ m Me}$	$\mathbf{Et}$	82(12)	1.4610(21)	88	$\mathrm{C}_9\mathrm{H}_{20}\mathrm{N}_2$	l
							1 10 0 5	1.01.1

• N: calcd, 17.93; found, 16.86. • Obtd via catalytic hydrogenation of **30**. • N: calcd, 14.27; found, 13.85. • Obtd as a mixt of cis and trans isomers in the ratio 90:10, resp, as shown by glpc. • 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. 'H: calcd, 12.75; found, 13.19. • 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. \* C: calcd, 71.68; found, 69.97. • Obtained as mixt of cis and trans isomers in the ratio 65:35 as shown by glpc. • C: calcd, 67.55; found, 66.95. \* Characterized as dipicrate, mp 227-228° dec. Anal. (C21H26N8O14) C, H, N. <sup>1</sup> Characterized as dipicrate, mp 180-181° dec. Anal. (C<sub>21</sub>H<sub>26</sub>N<sub>8</sub>O<sub>14</sub>) C, H, N.

nonane on to a 3.3 m  $\times$  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<sub>2</sub>O 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  $\delta$  1.12 and 1.45 (CH<sub>3</sub> of trans Me substituents); whereas the pmr spectrum ( $D_2O + DCl$ ) of the major isomer showed two doublets (J = 7 Hz) at  $\delta 1.02$  and  $1.27 \text{ (CH}_3 \text{ of cis Me substit-}$ uents). Guanylation of these isomeric amines via method A gave **12b** as the sulfate hemihydrate (75%), mp 294–295° dec [*Anal.* (C<sub>9</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S · 0.5H<sub>2</sub>O) C, H, N, S], and **12a** as the sulfate (48%), mp 292–295° (decomp) [*Anal.* (C<sub>9</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S) C, H, N, S].

The sulfate salt 12a was also obtained by fractional crystn from EtOH-H<sub>2</sub>O 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<sub>3</sub>. 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<sub>4</sub>) 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<sub>9</sub>H<sub>16</sub>N<sub>2</sub>) 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<sub>14</sub>H<sub>26</sub>N<sub>2</sub>) 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<sub>2</sub>O 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<sup>20</sup>D 1.5094 [lit.<sup>4</sup> bp 83-85° (1 mm); n<sup>20</sup>D 1.5067]. Anal. (C<sub>8</sub>H<sub>13</sub>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. ( $C_{13}H_{19}NO_{8}S$ ) 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<sub>2</sub> soln (210 ml, 2.24 moles) and the mixt was allowed to stand at room temp for 7 days. Solvent and excess MeNH<sub>2</sub> were removed under vacuum, 40% NaOH soln (10 ml, 0.1 mole) was added, and the soln was extd thoroughly with Et<sub>2</sub>O. After drying (MgSO<sub>4</sub>), the combined Et<sub>2</sub>O exts were evapd under vacuum and the crude oil was distd to give 52 (6.68 g, 46%): bp 67-69° (1 mm);  $n^{20}$ D 1.4995, characterized as the picrate, mp 158°. Anal. (C<sub>15</sub>H<sub>19</sub>N<sub>3</sub>O<sub>7</sub>) C, H, N.

1-(3-Aminopropyl)-2,4-dimethylpyrrolidine (53), 1-(8-Amino-1-octyl)-2,4-dimethylpyrrolidine (54), and 2,4-Dimethyl-1-(2methylaminoethyl)pyrrolidine (55).—The pyrroles (48, 49, and 52) were hydrogenated at room temp and 35.15 kg/cm<sup>2</sup> in EtOH and 5 N HCl with 5% Rh-Al<sub>2</sub>O<sub>3</sub> as catalyst. The hydrogenation mixts were worked-up in the usual way to give the aminoalkylpyrrolidines: 53 (66%), bp 82-86° (13 mm),  $n^{21}D$  1.4595, characterized as the dipicrate, mp 195-198° dec [Anal. (C<sub>21</sub>H<sub>26</sub>N<sub>5</sub>O<sub>14</sub>) C, H, N]; 54 (50%), bp 96° (0.35 mm),  $n^{22}D$  1.4620 [Anal. (C<sub>14</sub>H<sub>20</sub>N<sub>2</sub>) H, N; C: calcd, 74.27; found, 73.84; and 55 (66%), bp 89-90° (25 mm),  $n^{21}D$  1.4490, characterized as the dipicrate, mp 141-142° dec [Anal. (C<sub>21</sub>H<sub>26</sub>N<sub>8</sub>O<sub>14</sub>) 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<sub>2</sub>O 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  $60-65^{\circ}$  (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<sub>9</sub>H<sub>16</sub>N<sub>2</sub>) H, N; C: calcd, 71.01; found This mixt of pyrroles was fractionated through a stain-69.75]. less 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<sub>2</sub>O<sub>3</sub> 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<sub>8</sub>H<sub>20</sub>N<sub>2</sub>) C, H, N]. This mixt of pyrrolidines was seed by shortcolumn chromatog on silica gel G (elution with 4:1 EtOH-5 N NH<sub>4</sub>OH) to give 58 (0.83 g) and 59 (0.28 g). Compd 58 was the component with the highest  $R_i$  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.

 $N-2\cdot(2,4-\text{Dimethyl-1-pyrrolidinyl})$ ethyl- $N^1$ -nitroguanidine and Hydrochloride (16).—To a stirred soln of 42 (14.20 g, 0.1 mole) in 1:1 EtOH-H<sub>2</sub>O (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<sub>9</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub>) 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<sub>2</sub>O 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 2amino-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.<sup>22</sup> mp 162–165°) was prepd as described by Miller and Long<sup>22</sup> and was converted to phenylsuccinimide (mp 74–77°; lit.<sup>23</sup> mp 90°) by the method of Wegscheider and Hecht.<sup>23</sup> The succinimide was then reduced with LAH and worked-up in the usual way to give **60** (38%): bp 70–71° (0.7 mm);  $n^{23}D$  1.5528 [lit.<sup>24</sup> bp 92–94° (2 mm);  $n^{20}D$  1.5545].

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

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<sub>2</sub>O<sub>3</sub> catalyst (4 g). After 12 days, the catalyst was filtered off and AcOH was removed under vacuum. The residue was dissolved in H<sub>2</sub>O and the soln was basified with 40% NaOH soln and continuously extd with Et<sub>2</sub>O. Removal of Et<sub>2</sub>O and distn gave **61** (4.01 g, 39%): bp  $31-34^{\circ}$  (12 mm);  $n^{22}$ p 1.4380.

1-Cyanomethyl-2,5-dimethylpyrrolidine (62), 1-Cyanomethyl-2,3,4-trimethylpyrrolidine (63), and 1-Cyanomethyl-3-phenyl-pyrrolidine (64) (See Scheme IV).—2,5-Dimethylpyrrolidine (19.80 g, 0.2 mole) was dissolved in PhH (20 ml) contg Et<sub>8</sub>N (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<sub>8</sub>N · 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);  $n^{21}p$  1.4502. Anal. (C<sub>8</sub>H<sub>14</sub>N<sub>2</sub>) C, H, N.

Similarly, **61** was converted to **63** (60%), bp 110° (22 mm),  $n^{21}$ D 1.4538 [*Anal.* (C<sub>9</sub>H<sub>16</sub>N<sub>2</sub>) 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<sub>12</sub>H<sub>14</sub>N<sub>2</sub>) C, H, N].

1-(2-Aminoethyl)-2,5-dimethylpyrrolidine (65), 1-(2-Aminoethyl)-2,3,4-trimethylpyrrolidine (66), and 1-(2-Aminoethyl)-3phenylpyrrolidine (67) (See Scheme IV).—A soln of 62 (6.90 g, 0.05 mole) in Et<sub>2</sub>O (50 ml) was added dropwise to a stirred suspension of LAH (2.85 g, 0.075 mole) in Et<sub>2</sub>O (50 ml) under N<sub>2</sub>. At the end of the addn, the mixt was refluxed for 3 hr, allowed to cool, and H<sub>2</sub>O (2.85 ml), 15% NaOH soln (2.85 ml), and H<sub>2</sub>O (8.55 ml) were added. After filtration, the soln was dried (MgSO<sub>4</sub>), Et<sub>2</sub>O was removed under vacuum, and the crude oil was distd to give 65 (2.25 g, 32%): bp 65–66° (10 mm);  $n^{20.5p}$  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),  $n^{20}$ 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-piodobenzenesulfonamide (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<sub>2</sub>O. The aq phase was then adjusted to pH 9 by addn of 5 N HCl and extd thoroughly with Et<sub>2</sub>O. The combined Et<sub>2</sub>O exts were dried (MgSO<sub>4</sub>) 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<sub>14</sub>-H<sub>21</sub>BrN<sub>2</sub>O<sub>2</sub>S) 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.<sup>27</sup> bp 109° (20 mm),  $n^{20}$ D 1.4435] was prepared by the method of Colonge and Gelin.<sup>27</sup> The pentynoic acid (78.40 g, 0.70 mole) was then hydrated by treatment with a 5% solution of HgSO<sub>4</sub> in 10% H<sub>2</sub>SO<sub>4</sub> (700 ml) at 100° for 1 hr. After cooling, the solution was extd thoroughly with Et<sub>2</sub>O, the exts were dried (MgSO<sub>4</sub>) and evapd under vacuum, and distn afforded **70** (61.60 g, 68%): bp 106–114° (0.7 mm);  $n^{22}$ D 1.4398 [lit.<sup>28</sup> 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<sub>2</sub> 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<sub>3</sub>, basified with 40% NaOH soln, and extd thoroughly with CHCl<sub>3</sub>. After drying (MgSO<sub>4</sub>), 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<sub>8</sub>H<sub>18</sub>N<sub>2</sub>O) H, N; C: caled, 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<sub>2</sub>O (60 ml) was added dropwise to a stirred suspension of LAH (5.70 g, 0.15 mole) in Et<sub>2</sub>O (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<sub>2</sub>O gave the purified dipicrate, mp 204-209°. Anal. (C20H24N8O14) 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  $Et_2O_2$  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<sub>9</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S·H<sub>2</sub>O) C, H, N: S: calcd, 10.67; found, 11.20.

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