[Chem. Pharm. Bull. 15(7) 936~943 (1967)]

UDC 547.495.9

115. Tadakazu Tsuji, Hiroko Momona, and Takeo Ueda: Syntheses of Aminoalkylguanidine Derivatives.*1

(*Pharmaceutical Institute, Keio-Gijuku University**2)

The hydrochlorides of N^1-benzyl-2-methyl-1,2-propanediamine (I) and 5-amino-1,3-dibenzyl-5-methylhexahydropyrimidine (II) were debenzylated by the catalytic hydrogenation under pressure. 2-Methyl-1,2-propanediamine (III) which obtained from I, was derived to monoguanidine compound. The structure of this compound was concluded to be (2-amino-2-methylpropyl)guanidine from the comparison of the infrared spectra of related compounds. 2-Methyl-1,2,3-propanetriamine obtained from II, its starting material II, and other ethylenediamine derivatives were also guanidilated by the action of S-methylisothiourea sulfate.

(Received June 4, 1966)

In a previous paper,[1] the authors reported the synthesis of N^1-substituted 2-methyl-1,2-propanediamine and its guanidilation. This paper concerns the syntheses of 2-methyl-1,2-propanediamine and 2-methyl-1,2,3-propanetriamine by means of the debenzylation of the corresponding benzyl derivatives, and further describes the guanidilation of the above and related compounds.

Debenzylation of N^1-Benzyl-2-methyl-1,2-propanediamine and 5-Amino-1,3-dibenzyl-5-methylhexahydropyrimidine

Although the debenzylation of the free bases of N^1-benzyl-2-methyl-1,2-propanediamine (I) and 5-amino-1,3-dibenzyl-5-methylhexahydropyrimidine (II) was not taken place by the catalytic hydrogenation even under pressure,[2] their hydrochlorides were found to be debenzylated, as shown in Chart 1. 2-Methyl-1,2-propanediamine (III) was obtained from I. Products obtained from II were confirmed to be N^1-benzyl-2-methyl-1,2,3-propanetriamine (V) and 2-methyl-1,2,3-propanetriamine (VI). In a latter reaction, the first debenzylated product might be 5-amino-1-benzyl-5-methylhexahydropyrimidine (IV). It was already known that hexahydropyrimidines were readily hydrolyzed to propanediamine derivatives by acids.[3] Therefore, it could be said that the hydrochloride of IV was hydrolyzed to V, and V was partially debenzylated to VI. In fact, the hydrochloride of V was hydrogenated to yield VI.

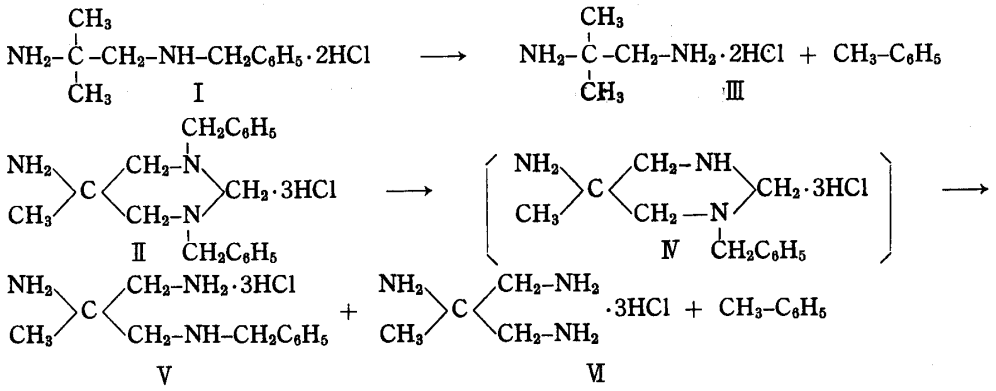


Chart 1.

*1 Presented at the Annual Meeting of Pharmaceutical Society of Japan (1965).

*2 Shinano-machi, Shinjuku-ku, Tokyo (辻 忠和, 百名弘子, 上田武雄).

1) T. Tsuji, T. Ueda: This Bulletin, **12**, 946 (1964).

2) M. Senkus: J. Am. Chem. Soc., **68**, 10 (1946).

3) G. W. Kenner, A. Todd: Heterocyclic Compound (R. C. Elderfield, ed.), Vol. VI, p. 315 (1957), John-Wiley & Sons, Inc., New York.

Guanidilation of 2-Methyl-1,2-propanediamine

Monoguanidilated product (Ⅶ) was yielded from the reaction of Ⅲ with S-methylisothiourea sulfate. In order to confirm the location of guanidinium group in this product, the infrared spectrum of Ⅶ was compared with those of Ⅲ and related known compounds. These data are shown in Table I and Ⅱ.

Table I. Infra Red Spectra of 1,2-Propanediamine and Related Compounds

Compound	1650～1500 cm^{-1}			
$(CH_3)_2CHCH_2NH_2\cdot\frac{1}{2}H_2SO_4$	1621			1510
$OHC(CH_3)_2CH_2NH_2\cdot\frac{1}{2}H_2SO_4$	1620			1508
$NH_2C(CH_3)_2CH_2N$(H)$\cdot H_2SO_4$	1630		1540	
$NH_2C(CH_3)_2CH_2N$(O)$\cdot H_2SO_4$	1630		1540	
$NH_2C(CH_3)_3\cdot\frac{1}{2}H_2SO_4$	1638	1620	1541	
$NH_2C(CH_3)_2CH_2OH\cdot\frac{1}{2}H_2SO_4$ (XV)	1635		1535	
$(CH_3)_2NH\cdot\frac{1}{2}H_2SO_4$	1630			
$NH_2C(CH_3)_2CH_2NHC_3H_7\cdot\frac{1}{2}H_2SO_4$	1630		1535	
$NH_2C(CH_3)_2CH_2NH_2\cdot H_2SO_4$ (Ⅲ)	1635		1540	1500
$RC(CH_3)_2CH_2NH_2\cdot\frac{1}{2}H_2SO_4$	1620			1510
$NH_2C(CH_3)_2CH_2R\cdot\frac{1}{2}H_2SO_4$	1630		1540	

Table Ⅱ. Infra Red Spectra of (2-Amino-2-methylpropyl)guanidine and Related Compounds

Compound	1750～1500 cm^{-1}						
	Guanidinium band					Others	
$(CH_3)_2CHCH_2NHC(=NH)NH_2\cdot\frac{1}{2}H_2SO_4$		1660					
$OHC(CH_3)_2CH_2NHC(=NH)NH_2\cdot\frac{1}{2}H_2SO_4$	(1730)[a]	1660					
$NH_2CNHC(=NH)NHC(CH_3)_2CH_2OH\cdot\frac{1}{2}H_2SO_4$	(1730)	1660		1570			
$[NH_2CNHC(=NH)NHC(CH_3)_2CH_2-]_2NH\cdot H_2SO_4\cdot H_2O$ (X)		1658		1570		1635	
$(CH_3)_2NC(=NH)NH_2\cdot\frac{1}{2}H_2SO_4$			1640		1530		
$NH_2CNHC(=NH)NHC(CH_3)_2CH_2N(C_3H_7)CNH_2\cdot H_2SO_4$		(1670) (1655)	1635	1570	1535	1510	
$NH_2CNHC(=NH)NHC(CH_3)_2CH_2N(C_6H_{13})CNH_2\cdot H_2SO_4$		(1672) (1655)	1635	1565	1540	1510	
$NH_2C(CH_3)_2CH_2NHC(=NH)NH_2\cdot H_2SO_4$ (Ⅶ)	1700	1660				1630	1540
$RC(CH_3)_2CH_2NHC(=NH)NH_2\cdot\frac{1}{2}H_2SO_4$		1660					
$NH_2CNHC(=NH)NHC(CH_3)_2CH_2R\cdot\frac{1}{2}H_2SO_4$		1660		1570			
$NH_2CNHC(=NH)NHC(CH_3)_2CH_2N(alkyl)CNH_2\cdot H_2SO_4$ (XII)		(1670) (1655)	1635	1570	1535	1510	

a) shoulder

As can be seen in Table I, two bands at 1635 and 1540 cm^{-1} in Ⅲ were assigned to N^+-H absorption of 2-amino group of Ⅲ, and other two bands at 1635 and 1500 cm^{-1}, to that of 1-amino group. In Ⅶ, there was observed the characteristic absorptions at 1630 and 1540 cm^{-1}, which suggested that Ⅶ might possess the NH_3^+-$C(CH_3)_2$-CH_2- moiety. From Table Ⅱ, the sulfate of -$C(CH_3)_2$-CH_2-NH-C(=NH)-NH_2-moiety showed the absorption at 1660 cm^{-1}. While, the sulfate of NH_2-C(=NH)-NH-$C(CH_3)_2$-CH_2- moiety absorbed at 1670~1655 and 1570 cm^{-1}. The compound Ⅶ possessed the absorption at 1660 cm^{-1}, but not any band at 1570 cm^{-1}. Thus, Ⅶ was concluded to be 2-(2-amino-2-methylpropyl)guanidine sulfate.

Previously, the authors described the guanidilation of 2-metylpropanediamine derivatives.[1] From those and the present results, the behavior of guanidilation of compound (Ⅷ) was summarized in Chart 2.

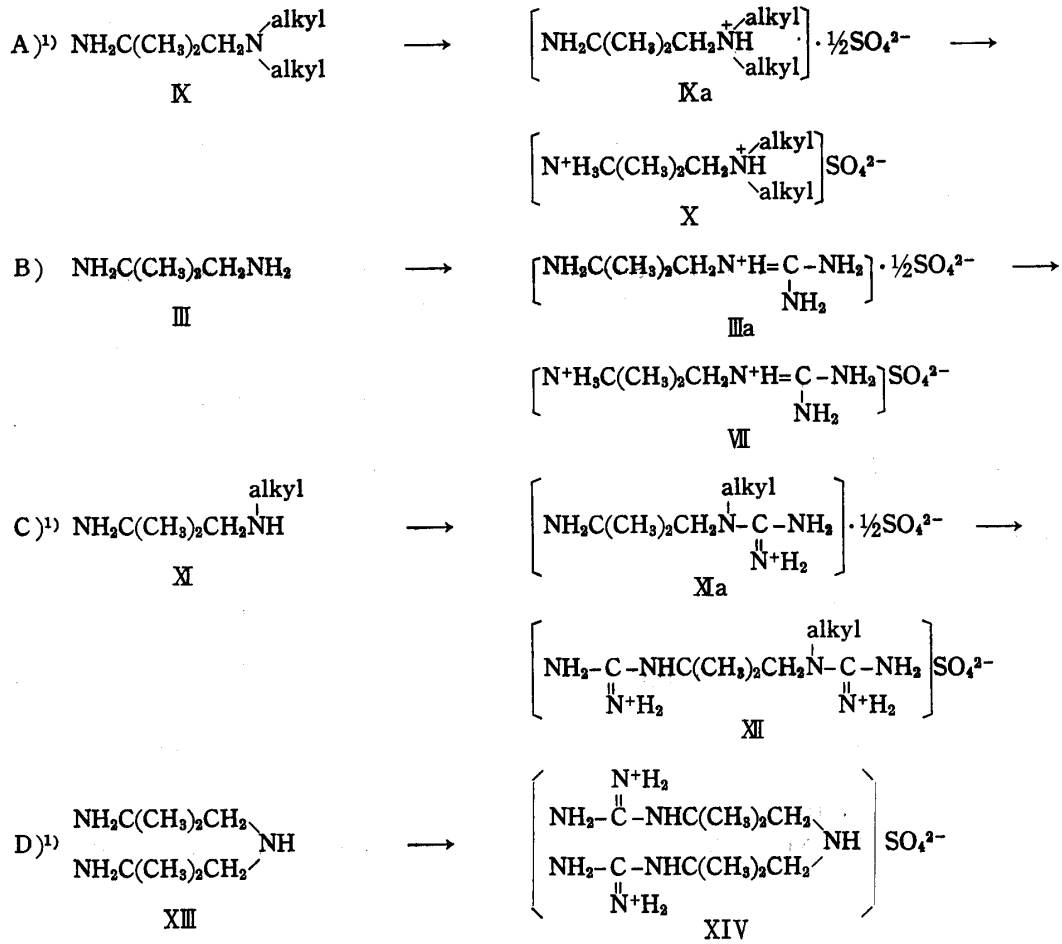


Chart 2. Reaction of $NH_2C(CH_3)_2CH_2NRR'$ (Ⅷ) with S-Methylisothiourea Sulfate

Among these reactions illustrated in Chart 2, equations (C) and (D) were the cases of successful guanidilation of steric hindered 2-amino group[1] of Ⅷ. On the contrary, in equations (A) and (B), 2-amino group of Ⅷ was not guanidilated, but converted merely to its sulfate.

Jencks[4] reported that the enhanced reactivity of the hydroxylamine hydroxyl group in the O-acylation might be due to the concerted attack or the intramolecular catalysis of the amino group. Furthermore, it was noted the intramolecular catalysis

4) W. P. Jencks : J. Am. Chem. Soc., **80**, 4585 (1958).

of hydroxyl group for the N-acylation of 2,2′-iminodiethanol and 2-anilinoethanol.[5] If the present aminolysis of S-methylisothiourea sulfate was assumed to proceed in a manner analogous to that[6,7] proposed for the aminolysis of carboxylic acid derivatives, it might be presumed the presence of intramolecular catalysis of neighboring hydroxyl or amino group.

In fact, the authors previously[1] reported that *tert.* butylamine was not derived to its guanidinium salt by the action of S-methylisothiourea sulfate but to its sulfate on account of the steric strain, while 2-amino-2-methylpropanol (XV) was able to guanidilate by the catalysis of 1-hydroxyl group.

In the same way, the catalysis of 1-amino group might be expected in the guanidilation of 2-amino group of Ⅷ. However, it might be necessary to take into account a case that the nitrogen atom of 1-amino group would react with S-methylisothiourea sulfate prior to the attack of this reagent on 2-amino group, and be converted to $\geqslant N^+H$ group. As the catalysis of amino group might be due to the lone pair of its nitrogen atom,[6] it might be certain that positively charged nitrogen atom did not show the catalysis. Therefore, the catalysis might not be expected in the above case. While, the catalysis might be expected in such cases as whether the attack of S-methylisothiourea sulfate on 2-amino group would occur prior to that on 1-amino group, or the nitrogen atom of 1-amino group would not be converted to positively charged one by the attack of S-methylisothiourea sulfate even though this attack might occur prior to that on 2-amino group. When considered these points, it might be possible to explain the contrasted results in the guanidilation of 2-amino group of Ⅷ according to the type of 1-amino group. For this purpose, the authors discussed the reaction of Ⅷ by dividing it into the following two cases.

(i) When 1-amino group of Ⅷ was not steric strained, the guanidilation of 2-amino group was not occurred from the following reason: Namely, this 1-amino group was converted to $\geqslant N^+H$ group by the action of S-methylisothiourea sulfate prior to the attack of this reagent on the steric strained 2-amino group. As $-N^+H$ group in (Ⅷa) occurred hereof might not catalyze the guanidilation of 2-amino group, it was certain that 2-amino group was not guanidilated by the steric strain and merely converted to its sulfate as same as the case of *tert.* butylamine. Equation (A)

$$\underset{\text{Ⅷ}}{NH_2C(CH_3)_2CH_2NRR'} \xrightarrow{CH_3SC(=NH)NH_2\cdot\frac{1}{2}H_2SO_4} \underset{\text{Ⅷa}}{[NH_2C(CH_3)_2CH_2N^+HRR']\cdot\frac{1}{2}SO_4^{2-}}$$

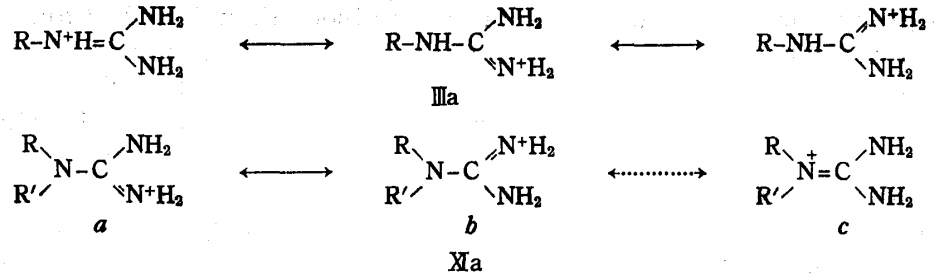
$$[N^+H_3C(CH_3)_2CH_2N^+HRR']SO_4^{2-} \xleftarrow{CH_3SC(=NH)NH_2\cdot\frac{1}{2}H_2SO_4}$$

Chart 3.

belonged to this case as shown in Table Ⅱ. Equation (B) also belonged to this case, and 1-amino group of Ⅲ was firstly guanidilated. As the positive charge resided partially on the nitrogen atom of 1-guanidinium group which was attached to methylene group in (Ⅲa) as shown in Chart 4, this nitrogen atom did not show the catalysis for the guanidilation of 2-amino group of Ⅲa. Therefore, 2-amino group of Ⅲa was only converted to its sulfate.

Equation (C) was the exception of case (i). As 1-alkylamino group of (Ⅺ) was not steric strained, this group was firstly guanidilated to give (Ⅺa). Different from Ⅲa,

5) G. Berti, G. Moretti, D. Segnini: Farmaco (Pavia) Ed. sci., **15**, 414 (1960). (C. A., **54**, 24515e (1960)).
6) M. L. Bender: Chem. Revs., **60**, 53 (1960).
7) J. F. Bunnett, G. T. Davis: J. Am. Chem. Soc., **82**, 665 (1960).

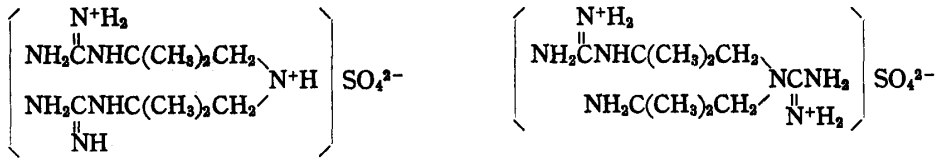


R-=$NH_2C(CH_3)_2CH_2$- R'-=C_nH_{2n+1}- (n=3, 4, 6)

Chart 4.

however, the positive charge was not localized on the nitrogen atom of 1-alkylguanidinium group which was attached to methylene group in XIa, since only two resonance structures, (*a*) and (*b*), for XIa were likely among the supposed three structures, (*a*), (*b*) and (*c*) in Chart 4. The resonance structure (*c*), in which $\overset{C}{C}\rangle N^+=C\langle\overset{N}{N}$ moiety might be required to possess a planar configuration, was prevented to form by the steric effect due to the close proximity of R, R' and two amino groups. Thus, this nitrogen atom catalyzed the guanidilation of 2-amino group in XIa to give (XII).

(ii) When 1-amino group in VIII was rather strongly steric strained than 2-amino group, the attack of S-methylisothiourea sulfate on 2-amino group might occur prior to that on 1-amino group. As uncharged 1-amino group showed the catalysis, 2-amino group of VIII was guanidilated successfully in this case. Equation (D) belonged to this case, because it seems certain from the scale model of (XIII) that 2-amino and 2-methyl groups could interfere with the front side approach of S-methylisothiourea sulfate to the nitrogen atom of 1-amino group. Therefore, the attack of S-methylisothiourea sulfate on 2-amino group occurred predominantly, and XIII was reacted with two mole of S-methylisothiourea sulfate to give (XIV) by the catalysis of unreacted 1-amino group. The structure of XIV was confirmed from the fact that its infrared spectrum showed the 2-guanidinium band at 1658 and 1570 cm^{-1}, and free NH frequency at 1635 cm^{-1}, as shown in Table II. The fact that no absoption of N^+H nor N^1-disubstituted guanidinium band was observed, excluded the following alternative structures.



Syntheses of Aminoethylguanidine Derivatives

1,3-Dibenzyl-5-guanidino-5-methylhexahydropyrimidine (XVI) was obtained from II with S-methylisothiourea sulfate. The success of the guanidilation of II might be due to the reason that two methylene groups of II were pulled back by the ring formation, and then 5-amino group was not suffered from any steric influence. Furthermore, IV was converted to the diguanidine derivative (XVII). The structure of XVII was assumed from the fact that it absorbed at 1660 (guanidinium band), 1630 and 1540 cm^{-1} (N^+-H absorptions).

The guanidine derivatives described hereof and in a previous paper,[1] were screened as to their antiviral activities on common cold virus and also hypotensive action. As the results, all compounds which possess *tert*-butyl guanidinium moiety did not show any antiviral and hypotensive actions, and VII which possess isobutyl guanidinium

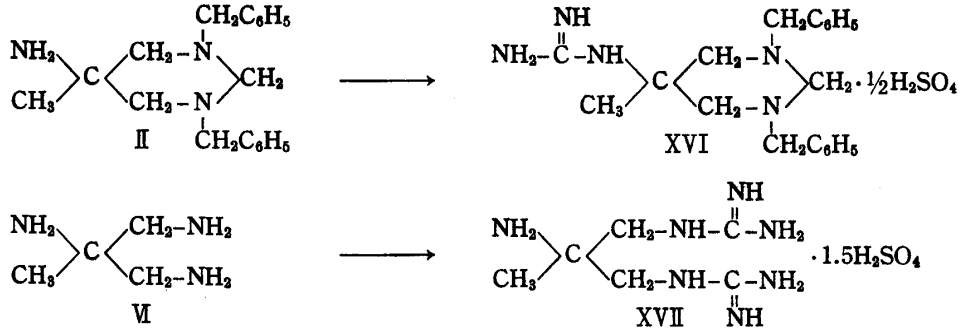


Chart 5.

moiety showed a weak antiviral activity. Ethylenediguanidine (XVIII) was found to possess the antiviral activity by our research group.[8] Furthermore, a number of N^1-amidino-N^2-substituted ethylenediamines were known to show the hypotensive action.[9] Therefore, it is of interest to examine the pharmacological activities of aminoethylguanidine derivatives for searching the antiviral and hypotensive drugs.

In connection with VII and XVIII, (2-aminoethyl)guanidine sulfate (XIX) and (2-isonicotinamidoethyl)guanidine sulfate (XX) were synthesized. Hydrolysis of (2-acetamidoethyl)guanidine sulfate, which was obtained from N-acetyl ethylenediamine, furnished XIX. Compound XX was synthesized from N-isonicotinoyl ethylenediamine (XXI) with S-methylisothiourea sulfate. Intermediate XXI was obtained from the reaction of methyl isonicotinate and ethylenediamine. In this reaction, N^1,N^2-diisonicotinoyl ethylenediamine was obtained as a by-product. The antiviral activities of both two compounds will be reported in future.

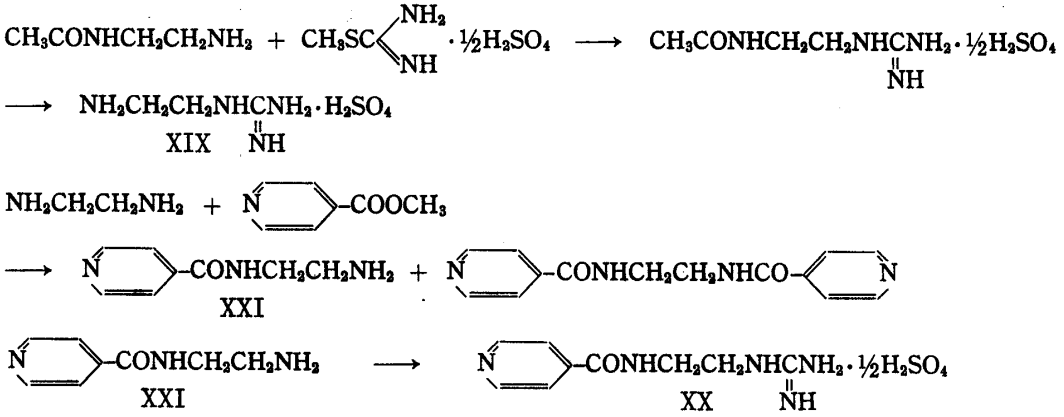


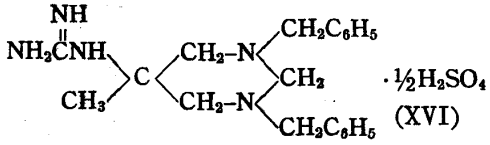
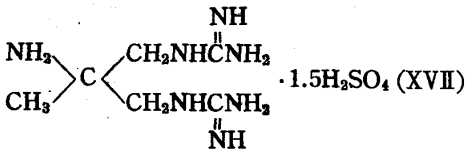
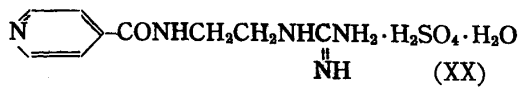
Chart 6.

Experimental

2-Methyl-1,2-propanediamine (III)——A solution of 17.8 g. of N^1-benzyl-2-methyl-1,2-propanediamine (I) in 70 ml. of 10% HCl was hydrogenated at 110~115° under pressure (100~120 kg./cm².) in the presence of Pd-C (Pd, 0.6 g.) for 3 hr. After removal of the catalyst by filtration, the filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in small amount of H_2O and made basic with anhyd. K_2CO_3. The separated oil was extracted with ether, dried over anhyd. K_2CO_3 and the solvent was removed by distillation. The remained oil was distilled at 113~115°(lit.,[1] b.p_{754} 115°) to give 4.3 g. of

8) A. Takada, T. Ueda: Keio J. Med., to be published.
9) *a*) R.A. Maxwell, A.J. Plummer, F. Schneider, H. Povalski, A.J. Daniel: J. Pharmacol. Exptl. Therap., **128**, 22 (1960); *b*) R.P. Mull, R.H. Mizzoni, M.R. Dapero, M.E. Egbert: J. Med. Pharm. Chem., **5**, 944 (1962); *c*) J.H. Short, U. Biermacher, D.A. Dunnigan, T.D. Leth: J. Med. Chem., **6**, 275 (1963).

Table Ⅲ. Guanidine Derivatives

Compound	Appearance	m.p. (decomp.) (°C)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$NH_2C(CH_3)_2CH_2NHCNH_2 \cdot H_2SO_4$ (Ⅶ) NH	prisms	(295)	$C_5H_{14}N_4 \cdot H_2SO_4$	26.31	7.07	24.54	26.38	7.09	24.74
$OHC(CH_3)_2CH_2NHCNH_2 \cdot \frac{1}{2}H_2SO_4$ NH	prisms	(287)	$C_5H_{13}ON_3 \cdot \frac{1}{2}H_2SO_4$	33.32	7.83	23.32	—	—	23.15
 (XVI)	fine needles	(185)	$C_{20}H_{27}N_5 \cdot \frac{1}{2}H_2SO_4$	62.15	7.30	18.12	—	—	18.07
 (XVII)	fine needles	(252)	$C_6H_{17}N_7 \cdot 1.5H_2SO_4 \cdot H_2O$	20.45	6.29	27.82	20.71	6.01	27.83
$CH_3CONHCH_2CH_2NHCNH_2 \cdot \frac{1}{2}H_2SO_4$ NH	needles	70～ 72	$C_5H_{12}ON_4 \cdot \frac{1}{2}H_2SO_4$	31.08	6.78	29.00	30.98	6.91	29.02
 (XX)	plates	174～175	$C_9H_{13}ON_5 \cdot H_2SO_4 \cdot H_2O$	33.43	5.30	21.66	33.78	5.61	21.85

colorless oil. *Anal.* Calcd. for $C_4H_{12}N_2$: N, 31.78. Found : N, 31.50. Dihydrochloride, colorless prisms, m.p. 298°. (from dil. EtOH). *Anal.* Calcd. for $C_4H_{14}N_2Cl_2$: C, 29.82; H, 8.76; N, 17.39. Found : C, 29.76; H, 8.90; N, 17.43.

2-Methyl-1,2,3-propanetriamine (VI) and its N^1-Benzyl Derivative (V)——5-Amino-1,3-dibenzyl-5-methylhexahydropyrimidine (II) (29.5 g.) was hydrogenated by the same procedure described above. The produced oil was distilled fractionally. The first fraction gave VI, b.p. 178~182°, as colorless oil (1.8 g.). *Anal.* Calcd. for $C_4H_{13}N_3$: N, 40.73. Found : N, 40.55. Trihydrochloride, colorless prisms, m.p. 275~276°(from AcOH). *Anal.* Calcd. for $C_4H_{16}N_3Cl_3 \cdot \frac{1}{2}H_2O$: C, 21.68; H, 7.73; N, 18.97. Found : C, 21.99; H, 7.91; N, 18.71. The second fraction gave V, $b.p_2$ 136°, as pale yellow oil (4.1 g.). *Anal.* Calcd. for $C_{11}H_{19}N_3 \cdot H_2O$: N, 19.89. Found : N, 20.20. V and VI were not decomposed when refluxed with 20% HCl for 1 hr. Benzoates of V and VI (oil substances) did not form picrates. From these results, V and VI were not presumed to be hexahydropyrimidine derivatives. When V was hydrogenated by the same procedure described above, VI was obtained in 61% yield.

General Procedure for Syntheses of Guanidine Derivatives——A solution of 0.01 mole of polyamine and 1.39 g. of S-methylisothiourea sulfate (for one primary or secondary amino group) in 40 ml. of H_2O, was heated on a steam bath for 2 hr., and then evaporated to dryness. The residue was recrystallized from H_2O or dil. EtOH. Compounds obtained hereof are shown in Table III.

N-Amidino Ethylenediamine Sulfate (XIX)——A solution of 1 g. of 2-acetamidoethylguanidine sulfate in 2.5 ml. of 10% H_2SO_4 was gently refluxed for 1 hr. and then evaporated to dryness on a water bath. The residue was recrystallized from H_2O to colorless prisms, m.p. 237~239°(decomp.). *Anal.* Calcd. for $C_3H_{10}N_4 \cdot H_2SO_4 \cdot \frac{1}{2}H_2O$: C, 17.22; H, 6.26; N, 26.78. Found : C, 17.13; H, 6.14; N, 26.55.

N-Isonicotinoyl Ethylenediamine (XXI)——A solution of 15.5 g. of methyl isonicotinate in 20.4 g. of ethylenediamine was heated on a water bath for 20 hr. After cooling, the precipitate (A) was separated from the filtrate (B). The precipitate (A), N^1,N^2-diisonicotinoyl ethylenediamine, was recrystallized from dioxane to colorless needles, m.p. 270~271°. Yield, 11.7 g. *Anal.* Calcd. for $C_{14}H_{14}O_2N_4$: C, 62.21; H, 5.22; N, 20.04. Found : C, 61.94; H, 5.01; N, 20.23.

From the filtrate (B), excess ethylenediamine was distilled off in vacuum on a water bath. The residual solid, XXI, was recrystallized from EtOAc to colorless pillars, m.p. 101~103°. Yield, 7.9 g. *Anal.* Calcd. for $C_8H_{11}ON_3$: C, 58.16; H, 6.71; N, 25.44. Found : C, 57.77; H, 6.15; N, 25.62.

10) H. Reihlen, G. Hessling, W. Hühn, E. Weimbrenner : Ann., **493**, 20 (1932).