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132. Tadakazu Tsuji and Takeo Ueda : Syntheses of 2-Guanidino-2-methylpropylamine Derivatives.

(*Pharmaceutical Institute, Keio-Gijuku University*[*1])

As reported in the previous papers,[1] our group found that 2-imino-4,6-dimethyl hexahydro-*s*-triazine nitrate, guanidine salts and ethylenediguanidine exerted inhibitory effects on some pathogenic viruses in tissue culture. Based on these findings, the authors conceived an idea to synthesize 2-guanidino-2-methylpropylamine derivatives having a related structure to the above compounds.

The compounds of this type are of interest for finding not only antiviral agents, but also hypertensive drugs. This paper describes the syntheses of 2-guanidino-2-methylpropylamine derivatives.

Senkus[2] has shown that N-hydroxymethylalkylamines react with secondary nitroparaffins to give the nitro amines. According to his work, the separation of resulted nitro amines were found rather troublesome and needed long days, and the distillation of nitro amines often caused the decomposition. However, the authors found that the nitro amines were readily isolated as hydrochlorides, by means of the following improved method. This improved method was carried out by warming the amines, formaldehyde and 2-nitropropane, followed by isolating the nitro amines as hydrochlorides. The reaction is shown by the following chart :

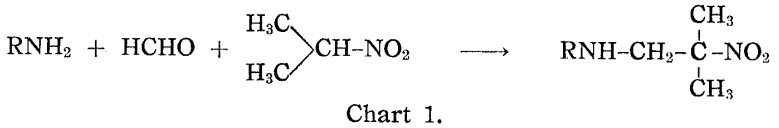


Chart 1.

Among these reactions, the unusual result was obtained, when guanidine was used in lieu of an amine; namely, unexpected bis(2-methyl-2-nitropropyl)amine was obtained in 59% yield, and expected 1,3-bis(2-methyl-2-nitropropyl)guanidine was obtained in 7% yield, as illustrated in the next Chart 2.

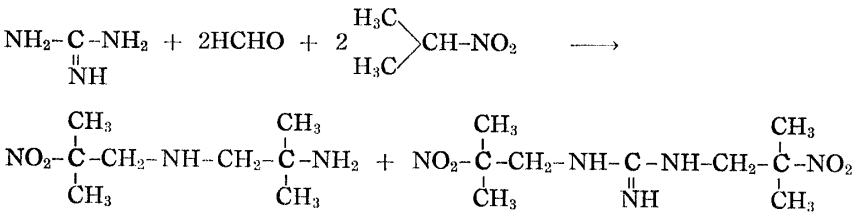


Chart 2.

N-Substituted 2-methyl-2-nitropropylamine hydrochlorides obtained hereof are listed in Table I.

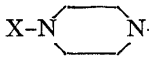
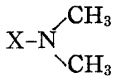
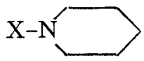
The above nitro amines were hydrogenated to the corresponding polyamines in the presence of palladium carbon catalyst under pressure. 2-Methyl-1,2-propanediamine derivatives thus obtained are summarized in Table II.

*1 Shinano-machi, Shinjuku-ku, Tokyo (辻 忠和, 上田武雄).

1) T. Ueda, S. Toyoshima, T. Tsuji, S. Watanabe : This Bulletin, **10**, 1167 (1962); S. Toyoshima, T. Ueda, T. Tsuji, Y. Seto, J. Nomoto : *Ibid.*, **11**, 5 (1963); T. Ueda, S. Toyoshima, A. Takada, Y. Seto : Papers read at the Kanto Local Meeting of Pharmaceutical Society of Japan, July, 1962, Tokyo.

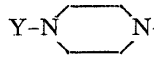
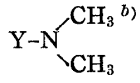
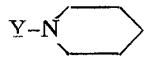
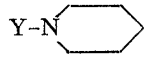
2) M. Senkus : J. Am. Chem. Soc., **68**, 10 (1946).

TABLE I. N-Substituted 2-Methyl-2-nitropropylamine Hydrochlorides

Compound	Appearance	m.p. (°C) (decomp.)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR in KBr (cm^{-1})
X[a]-NH-X·HCl	needles	(182~183)[b]	$C_8H_{17}O_4N_3$·HCl	—	—	16.43	—	—	16.22	1550 1345
X-NH-C(=NH)-NH-X·HCl	plates	125~126	$C_9H_{19}O_4N_5$·HCl	36.30	6.77	23.73	36.64	6.90	23.91	1550 1346
X-NH-CH_2·2HCl X-NH-CH_2	〃	(228)	$C_{10}H_{22}O_4N_4$·2HCl	35.83	6.90	16.71	36.01	6.84	16.53	1550 1345
X-NH-C_3H_7·HCl	〃	152~154	$C_7H_{16}O_2N_2$·HCl	42.74	8.71	14.24	42.51	8.42	14.11	1550 1345
X-NH-C_4H_9·HCl	needles	157~159	$C_8H_{18}O_2N_2$·HCl	45.60	9.09	13.30	45.38	8.81	13.41	1550 1342
X-NH-C_6H_{13}[2]	—	—	$C_{10}H_{22}O_2N_2$	—	—	13.85	—	—	—	—
	needles	169~170	$C_{12}H_{24}O_4N_4$	—	—	19.43	—	—	19.31	1530 1340
	prisms	189~191	$C_6H_{14}O_2N_2$·HCl	39.45	8.28	15.34	39.78	8.40	15.08	1550 1345
	plates	170~172	$C_9H_{18}O_2N_2$·HCl	—	—	12.58	—	—	12.77	1548 1342

a) X = NO_2-C(CH_3)(CH_3)-CH_2- b) lit.,[1] m.p. 178°(decomp.)

TABLE II. 2-Methyl-1,2-propanediamine Derivatives

Compound	b.p. of free base (°C/mm.)	Appearance of salt	m.p. (°C) (decomp.)	Formula	Analysis (%) Calcd.	Found
Y[a]-NH-Y	110~120/125	—	—	$C_8H_{11}N_3$	26.39	26.22
Y-NH-C(=NH)-NH-Y·3HCl	—	needles	(182~184)	$C_9H_{23}N_3$·3HCl	22.54	22.28
Y-NH-CH_2·4HCl Y-NH-CH_2	—	〃	(214)	$C_{10}H_{26}N_4$·4HCl	16.09	15.99
Y-NH-C_3H_7·2HCl	85/175	〃	243~347	$C_7H_{18}N_2$·2HCl	13.79	13.57
Y-NH-C_4H_9[2]	64~66/10	—	—	$C_8H_{20}N_2$	19.42	—
Y-NH-C_6H_{13}[2]	72/10	—	—	$C_{10}H_{24}N_2$	16.26	—
	—	prisms	(222)	$C_{12}H_{28}N_4$·2H_2SO_4	13.20	13.38
	119/755	—	—	$C_6H_{16}N_2$	24.11	—
	60.5/6[b]	prisms	252~254	$C_9H_{20}N_2$·2HCl	12.22	12.46
	60.5/6[b]	plates	198	$C_9H_{20}N_2$·½H_2SO_4	C 52.65 H 10.31 N 13.65	C 52.43 H 10.07 N 13.34

a) Y = NH_2-C(CH_3)(CH_3)-CH_2- b) H.G. Johnson: J. Am. Chem. Soc., **68**, 12 (1946).

The above polyamines were reacted with S-methylisothiourea to obtain the corresponding guanidine derivatives. By this reaction, bis(2-amino-2-methylpropyl)amine and N,N′-bis(2-amino-2-methylpropyl)ethylenediamine were converted to the diguanidine compounds, respectively, as shown in Chart 3. From N′-alkyl-2-methyl-1,2-propanediamine, where alkyl group was propyl, butyl or hexyl group, the diguanidine compound was obtained, and any monoguanidine compound was not afforded.

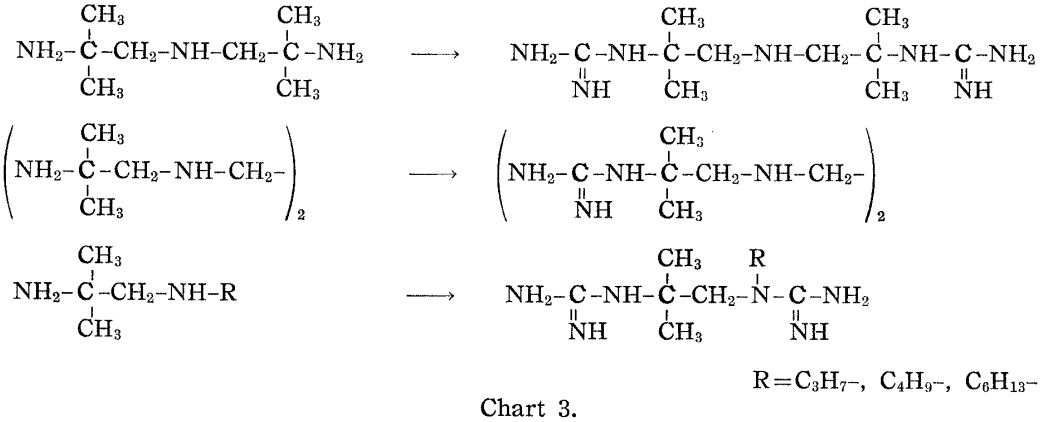


Chart 3.

On the other hand, the reaction of 1,4-bis(2-amino-2-methylpropyl)piperazine (I), N′-dimethyl-2-methyl-1,2-propanediamine (II) or 1-(2-amino-2-methylpropyl)piperidine (III) with S-methylisothiourea sulfate did not afford the expected guanidine compound, but the sulfate of I, II or III. This result was in marked contrast to the fact that

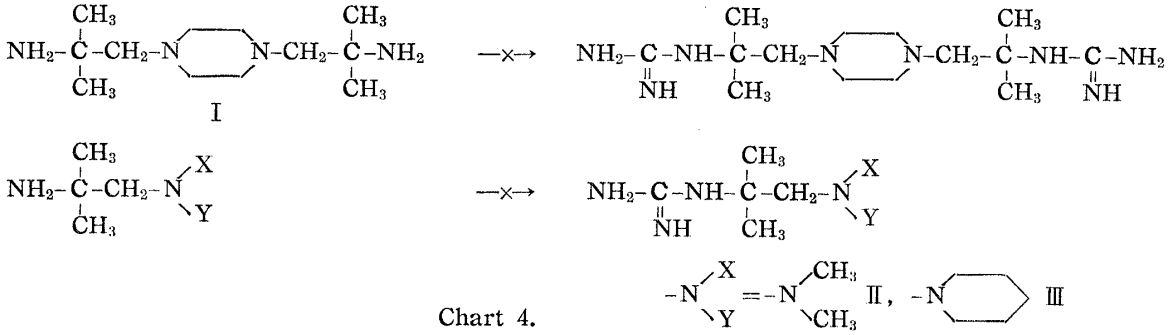
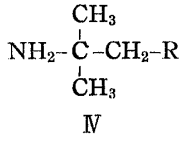


Chart 4.

1-(2-aminoethyl)piperidine was succeeded in guanidination with S-methylisothiourea sulfate.[3]

In connection with the guanidination of the above polyamines (IV, R=N< group), 2-amino-2-methylpropanol (IV, R=hydroxyl group) and *tert*-butylamine (IV, R=hydrogen) were treated with S-methylisothiourea sulfate. 2-Amino-2-methylpropanol were converted to the guanidine compound. While, *tert*-butylamine was found to be converted to its sulfate, but not to *tert*-butylguanidine. The unsuccessful guanidination of *tert*-butylamine might be due to the steric strain, which was caused by the bulky *tert*-butyl group. It is of interest that the reaction of the amine (IV, R=alkylamino or hydroxyl group) with S-methylisothiourea sulfate was not suffered from any interference, and gave the corresponding guanidine compound.



IV

II or III was found to be reactive with benzoylthiocyanate, but not with thiocyanic acid. The attempt to prepare the guanidine compounds from these thiourea derivatives

3) T. Ueda, K. Ishizaki, S. Kobayashi: Papers read at the Annual Meeting of Pharmaceutical Society of Japan, April, 1964, Tokyo.

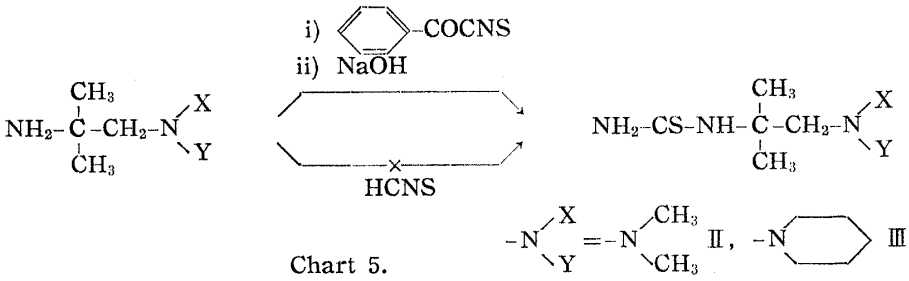


Chart 5.

via S-methylisothiourea derivatives, resulted to obtain the viscous masses. These structures were not confirmed yet. The hydrolysis of the benzoyl derivatives of 1-(2-guanidino-2-methylpropyl)piperidine, which was obtained by the reaction of III with benzoylcyanamide, resulted to yield III.

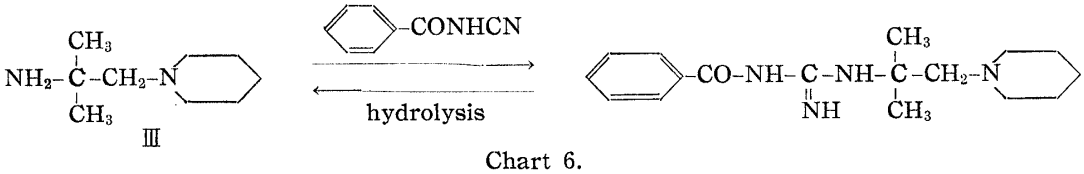


Chart 6.

The guanidine derivatives obtained hereof, are listed in Table III. All compounds listed in Table III, were positive for Sakaguchi test. The pharmacological properties of these guanidine compounds will be reported in another paper.

TABLE III. 2-Guanidino-2-methylpropylamine Derivatives

Compound	Appearance	m.p. (°C) (decomp.)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	IR in KBr (cm^{-1}) $\nu_{C=N}$
Z[a]-NH-Z·H_2SO_4·H_2O	prisms	(245)	$C_{10}H_{25}N_7 \cdot H_2SO_4 \cdot H_2O$	33.41	8.13	27.27	33.61	8.31	27.22	1670
Z-NH-CH_2·H_2SO_4	needles	(301)	$C_{12}H_{30}N_8 \cdot H_2SO_4$	—	—	29.14	—	—	28.99	1665
Z-NH-CH_2 / C_3H_7 / Z-N-C-NH_2·H_2SO_4 / NH	prisms	(214)	$C_9H_{22}N_6 \cdot H_2SO_4$	34.60	7.75	26.89	34.89	7.85	27.04	1672 1655
C_4H_9 / Z-N-C-NH_2·H_2SO_4 / NH	〃	(193~194)	$C_{10}H_{24}N_6 \cdot H_2SO_4$	36.79	8.03	25.75	36.53	7.99	25.69	1670 1648
C_6H_{13} / Z-N-C-NH_2·H_2SO_4 / NH	plates	162~164	$C_{12}H_{28}N_6 \cdot H_2SO_4$	—	—	23.71	—	—	23.85	1670 1655
Z-OH·$\frac{1}{2}H_2SO_4$	prisms	(289)	$C_5H_{13}ON_3 \cdot \frac{1}{2}H_2SO_4$	—	—	23.32	—	—	23.19	1670

a) Z=NH_2-C(=NH)-NH-C(CH_3)$_2$-CH_2-

Experimental

General Procedure for Synthesis of N-Substituted 2-Methyl-2-nitropropylamine Hydrochloride ——To a solution of 0.2 mole of amine and 19.8 g. of 2-nitropropane, 16.6 g. of 36% aq. HCHO was added dropwise under cooling by an ice-water bath. After the whole was warmed on a water bath for

1 hr., the separated oil was extracted with Et_2O, and then HCl gas was introduced into the etheral solution. The precipitate was collected and recrystallized from EtOH or H_2O.

When guanidine was employed in lieu of an amine, two products were obtained, as shown in Chart 2. Both two products were separated by treating with dioxane. Bis(2-methyl-2-nitropropyl)amine hydrochloride (59% yield) was insoluble in dioxane, and 1,3-bis(2-methyl-2-nitropropyl)guanidine hydrochloride (7% yield) was soluble in dioxane. Each compound was recrystallized from AcOH. Bis(2-methyl-2-nitropropyl)amine hydrochloride was identical with the authentic sample[4] by comparison of the IR spectra.

General Procedure for Synthesis of 2-Methyl-1,2-propanediamine Derivative——N-Substituted 2-methyl-2-nitropropylamine hydrochloride (0.1 mole) was dissolved in 80 ml. of H_2O and the solution was hydrogenated at 80~90° under pressure (100~120 kg./cm^2) in the presence of Pd-C. After removal of the catalyst by filtration, the solution was acidified with HCl and evaporated to dryness under reduced pressure. The residue was purified by recrystallization directly or made basic with K_2CO_3 and the separated oil was distilled in vacuum.

General Procedure for Synthesis of 2-Guanidino-2-methylpropylamine Derivative——A solution of 0.01 mole of polyamine and 1.39 g. of S-methylisothiourea sulfate (for one amino group) in 40 ml. of H_2O, was allowed to stand at room temperature for 3 hr., and then evaporated to dryness on a water bath. The residue was recrystallized from H_2O or dil. EtOH.

1-(2-Piperidino-1,1-dimethylethyl)thiourea——A solution of 3.3 g. of benzoylthiocyanate in 30 ml. of Me_2CO was added slowly into a solution of 3.1 g. of 1-(2-amino-2-methylpropyl)piperidine in 30 ml. of Me_2CO. The mixture was refluxed for an additional 5 min. After evaporation of the solvent, the residue was refluxed for 2 hr. with 18 ml. of 5% aq. NaOH. The solution was then acidified with HCl and the precipitate was removed off by filtration. The filtrate was shaken with Et_2O and the aqueous layer was made basic with NH_4OH. The resulted precipitate was recrystallized from H_2O to colorless pillars, m.p. 192~193°. *Anal.* Calcd. for $C_{10}H_{21}N_3S$: C, 55.77; H, 9.83; N, 19.53. Found: C, 55.53; H, 9.68; N, 19.51.

A mixture of 540 mg. of 1-(2-piperidino-1,1-dimethylethyl)thiourea and 320 mg. of Me_2SO_4 was heated at 150° in an oil bath for 1 hr. After cooling, the whole was added in 20 ml. of 20% NH_3-water, and evaporated to dryness on a water bath. The residual viscous mass was negative for Sakaguchi test, and unsuccessful in obtaining a crystalline substance.

1-(2-Dimethylamino-1,1-dimethylethyl)thiourea——This was prepared from N^1,N^1-dimethyl-2-methyl-1,2-propanediamine by the same procedure described above. Recrystallization from EtOH gave colorless needles, m.p. 119~120°. *Anal.* Calcd. for $C_7H_{17}N_3S$: C, 47.96; H, 9.78; N, 23.97. Found: C, 47.68; H, 9.59; N, 23.93.

1-Benzoyl-3-(2-piperidino-1,1-dimethylethyl)guanidine Hydrochloride——A solution of 0.01 mole of 1-(2-amino-2-methylpropyl)piperidine dihydrochloride and 1.46 g. of benzoylcyanamide in 120 ml. of EtOH was refluxed for 4 hr., and then evaporated to dryness. The residue was recrystallized from dil. EtOH to colorless plates, m.p. 202~203°. *Anal.* Calcd. for $C_{17}H_{24}ON_4Cl$: N, 16.53. Found: N, 16.51.
Hydrolysis: This compound (0.5 g.) was refluxed with 10 ml. of 5% HCl for 1 hr. After cooling, the solution was shaken with Et_2O. The water layer was separated and evaporated to dryness under diminished pressure. The residue was recrystallized from dil. EtOH to colorless prisms, m.p. 252~254°. This was identical with the sample of 1-(2-amino-2-methylpropyl)piperidine dihydrochloride by comparison of the IR spectra. *Anal.* Calcd. for $C_9H_{22}N_2Cl_2$: N, 12.22. Found: N, 12.10.

The authors' sincere thanks are due to U.S. Army Research and Development Group (Far East) for the kind support.

Summary

The polyamines which were obtained by the hydrogenation of N-substituted 2-methyl-2-nitropropylamines, were derived to the corresponding guanidine derivatives with S-methylisothiourea sulfate. Some polyamines were not derived to the guanidine compound, but to the sulfates of starting materials. The material 2-methyl-2-nitropropylamines were prepared by the condensation of 2-nitropropane, formaldehyde and amines.

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4) J. K. N. Jones, T. Urbanski: J. Chem. Soc., **1949**, 1766.