ii) by the Kiliani Mixture[11]: I (10 mg.) was dissolved in the Kiliani mixture (AcOH–H_2O–conc. H_2SO_4 =35:55:10; 1 ml.) and was heated on a water-bath for 1 hr. Water (1 ml.) was then added and the filtrate was neutralized with Amberlite IR-4B. Evaporation of the aq. solution gave yellow syrup which was revealed to contain L-rhamnose (Rf 0.58) on the paper (Toyo Roshi No. 51) chromatography using AcOEt–Pyridine–H_2O (2:1:2) and aniline hydrogen phthalate as a solvent and developer respectively.

Isolation of Nitrogen Compound (II)——Fraction 6 shown in Table II afforded colorless needles, m.p. 189.5~190.5°, recrystallized from MeOH–$CHCl_3$. Molecular weight determined by the Rast method was shown as revealed 400±20. *Anal.* Calcd. for $C_{16}H_{24}O_8N_4$ (M. W. =400.38): C, 47.99; H, 6.04; N, 13.99. Found: C, 47.82; H, 5.93; N, 14.07. UV λ_{max}^{EtOH} mμ (log ε): 209 (4.17), 268 (4.17). IR ν_{max}^{KBr} cm^{-1}: 3310, 3020, 2830, 1710, 1660, 1479, 1435, 1315, 1289, 1273, 1252, 1222, 1120, 1098, 1065, 1010, 906, 869, 851.

The authors express their deep gratitude to Prof. S. Wakayama, Hokkaido Gakugei University and students of Toyoni and Tomioka Junior High Schools for collecting materials. They are also indebted to Mrs. T. Tohma and Miss A. Maeda of the analytical laboratory of this Faculty for elemental analysis.

11) H. Kiliani: Ber., **63**, 2866 (1930).

[Chem. Pharm. Bull. 15(2) 228~232 (1967)]

UDC 547.495.9.07 : 615.77

Takeo Ueda and Kumi Ishizaki: Syntheses of 3-Aminopropylguanidine Derivatives.

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

The fourteen compounds of 3-(substituted amino)propylguanidine were synthesized by reacting S-methylisothiourea sulfate with 3-(substituted amino)propylamine: 3-(substituted amino) propylamine having an aliphatic substituent group at 3-position were synthesized by reacting the aliphatic amine with acrylonitrile and by reducting with lithium aluminum hydride, while 3-(substituted amino)propylamine having an aromatic substituent group at 3-position, synthesized by the Ing-Manske modification of the Gabriel synthesis of primary amines.

(Received May 12, 1966)

Recently, we have found that guanidine salts[1] and their related compounds[2] exerted inhibitory effect on several pathogenic viruses in tissue culture. In those studies, many compounds having guanidino moiety were synthesized and examined as to their antiviral activity. At the same time, attempts were also made to find pharmacologically active agents among those compounds. Especially, it was noted that some compounds of aminoalkylguanidine were found to have hypertensive and analgesic activities.

This finding prompted the authors to synthesize compounds of substituted amino-alkylguanidine.

This report is concerned with the syntheses of 3-(substituted amino)propylguanidine.

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1) T. Ueda, S. Toyoshima, T. Tsuji, Y. Seto, J. Nomoto: Keio J. Med., **10**, 257 (1961); Antibiotics and Chemotherapy, **XII**, 330 (1962).

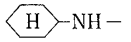
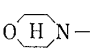
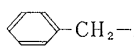
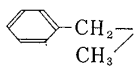
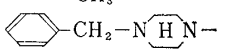
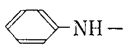
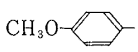
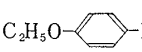
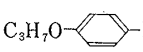
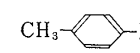
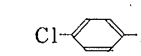
2) M. Furukawa, S. Toyoshima, T. Ueda: This Bulletin, **11**, 1247 (1963).

Sulfate of 2-heptamethyleneiminoethylguanidine[3] has been claimed as a hypertensive drug named Guanethidine among compounds of substituted aminoalkylguanidine.

Some compounds of substituted aminoethylguanidine[4] were synthesized and screened as to their pharmacological activity, and 2-(4-ethylpiperidino)ethylguanidine were selected as the most hypertensive agent among these compounds. Its analgesic effectiveness, however, was found comparatively lower.

After that, bis(guanidinopropyl)amine[5] synthesized by our group was found to have a favorite analgesic effect, compared with known non-narcotic analgeticas, although the mode of action of this agent has not been clarified yet. This finding suggested that the analgesic action of 2-(substituted amino)ethylguanidine might be increased by the introduction of propyl group in lieu of ethyl. According to this

Table I. $R-CH_2-CH_2-CH_2-NH_2$

R	Yield (%)	b.p. (°C)/mm. Hg	Formula	Analysis N (%) Calcd.	Found
$(CH_3)_2CH-NH-$	28	95/95[a]	$C_6H_{16}N_2$	24.11	24.45
	53	120~123/20[b]	$C_9H_{20}N_2$	17.93	18.26
	30	103~104/33[c]	$C_8H_{18}N_2$	19.70	19.93
	26	100~102/16[d]	$C_7H_{16}ON_2$	18.17	18.28
	27	121~122/5.5[e]	$C_{10}H_{16}N_2$	17.06	16.82
	57	118~119/4[f]	$C_{11}H_{18}N_2$	15.72	15.59
	30	154/5[g]	$C_{14}H_{23}N_3$	18.01	17.86
	39	130~132/6[h]	$C_9H_{14}N_2$	18.65	18.91
	21	119/14	$C_{10}H_{16}ON_2$	15.54	15.39
	28	180/10	$C_{11}H_{18}ON_2$	14.42	14.34
	32	162~167/6	$C_{12}H_{20}ON_2$	13.45	13.30
	20	129~130/4	$C_{10}H_{16}N_2$	17.06	17.28
	17	154~5/5	$C_9H_{13}N_2Cl$	15.17	14.99

a) Tarbell, *et al.*[7] reported dipicrate m.p. 185~186.5°.
b) Tarbell, *et al.* reported dipicrate m.p. 182.5~183.5°.
c) Sen, *et al.*[8] reported b.p. 88°/1 mm. Hg, picrate m.p. 208~9°.
d) Sen, *et al.* reported b.p. 92~93°/1 mm. Hg, picrate m.p. 165°.
e) Surrey, *et al.*[9] reported b.p. 98~102°/1 mm. Hg.
f) Shapiro, *et al.*[10] reported b.p. 80~81°/0.1 mm. Hg.
g) Caldwell[11] reported b.p. 116~119°/0.1 mm. Hg.
h) Bekhli, *et al.*[12] reported b.p. 126~129°/3 mm. Hg.

7) D.S. Tarbell, N. Shakespeare, C.J. Claus, J.F. Bunnett: J. Am. Chem. Soc., **68**, 1217(1946).
8) A.B. Sen, Y.D. Kulkarni: J. Indian Chem. Soc., **35**, 205(1958).
9) A.R. Surrey: J. Am. Chem. Soc., **71**, 3354(1949).
10) S.L. Shapiro, I.M. Rose, L. Freedman: J. Am. Chem. Soc., **81**, 3083(1959).
11) A.G. Caldwell: Brit. Pat., 997,036(1965) (C.A., **64**, 740e (1966)).
12) A.F. Bekhli, A.G. Serebrennikov: J. Gen. Chem., **19**, 1553(1949).

3) New and Non-official Remedy, 354 (1963).
4) T. Ueda, S. Akihama: Unpublished.
5) T. Ueda, S. Watanabe: Jap. Pat., 470,947 (1966).

assumption, the synthesis of 3-substituted aminopropylguanidine was undertaken, which had not been revealed in any literature to date.

The synthetic process of the objective 3-substituted aminopropylguanidine was considered to be consisted of (1) the synthesis of 3-substituted 1,3-propane diamine and (2) the guanidilation thereof.

For the synthesis of 3-substituted 1,3-propyldiamine, it was conceived to react amines with acrylonitrile and reduce the resulting products of substituted aminopropionitrile as shown in Chart 1.

$$R\text{-}NH_2 + CH_2{=}CH\text{-}CN \longrightarrow R\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CN$$

$$R\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CN + 4H \longrightarrow R\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2$$

R=substituent group

Chart 1.

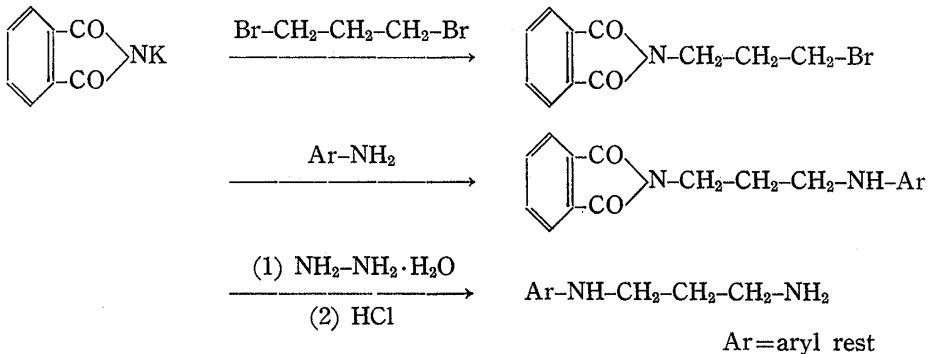
J. A. Harpham, *et al.*[6] synthesized 3-cyclohexylaminopropylamine by the reaction of cyclohexylamine with acrylonitrile and the reduction of the resulting product with hydrogen in the presence of Raney nickel.

According to this method, several compounds of N-substituted amines with acrylonitrile, and the nitriles were converted to 3-(substituted amino)propylamines by the reduction with lithium aluminum hydride in lieu of hydrogen and Raney nickel. The former reducing agent was found more preferable to the latter for the reduction.

The method described above was, however, found unsuitable for the preparation of 3-arylamino derivatives, because the selection of appropriate catalyst was very troublesome in the cyanoethylation of arylamine.

The repeated experimental results by the authors pointed to the possibility that the Ing-Manske modification of the Gabriel synthesis of primary amines was effective for the synthesis of 3-arylaminopropylamine. Thus, N-(arylaminopropyl)phthalimide prepared through the reaction of N-(3-bromopropyl)phthalimide with an arylamine, was reacted with ethanolic hydrazine hydrate, followed by the reaction with hydrochloric acid to yield the objective diamine, as shown in Chart 2.

The diamines synthesized are listed in Table 1.



Ar=aryl rest

Chart 2.

Next, compounds of 3-(substituted amino)propylamine synthesized by the above two methods were converted to corresponding propylguanidines by the guanidilation with S-methylisothiourea sulfate, as shown in Chart 3.

$$R\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH_2 + NH{=}C(S\text{-}CH_3)\text{-}NH_2 \longrightarrow R\text{-}NH\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}NH\text{-}C(=NH)\text{-}NH_2$$

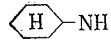
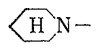
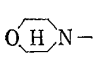
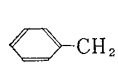
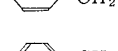
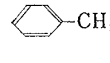
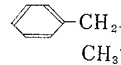
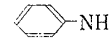
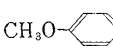
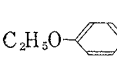
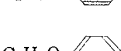
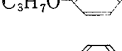
R=substituent group

Chart 3.

6) J. A. Harpham, R. J. J. Simkins, G. F. Wright : J. Am. Chem. Soc., **72**, 341 (1950).

The compounds synthesized are summarized in Table II.

Table II. R-CH_2-CH_2-CH_2-NH-C(=NH)-$NH_2 \cdot n H_2SO_4$

R	Yield (%)	m.p. (°C)	Appearance	Formula	Analysis N (%) Calcd.	Found
$(CH_3)_2N-$	97	300	prisms	$C_6H_{16}N_4 \cdot H_2SO_4$	23.12	23.29
$(CH_3)_2CH-NH-$	94	299	〃	$C_7H_{18}N_4 \cdot H_2SO_4$	21.86	21.70
	98	275	〃	$C_{10}H_{22}N_4 \cdot H_2SO_4$	18.91	19.10
	57	287	〃	$C_9H_{20}N_4 \cdot H_2SO_4$	19.84	19.85
	86	286	〃	$C_8H_{18}ON_4 \cdot H_2SO_4$	19.70	19.66
	96	260～261	〃	$C_{11}H_{18}N_4 \cdot H_2SO_4$	18.41	18.41
	79	285～286	〃	$C_{15}H_{25}N_5 \cdot H_2SO_4$	18.75	19.09
	99	181～182	〃	$C_{12}H_{20}N_4 \cdot \frac{1}{2}H_2SO_4$	20.81	20.80
	74	194～196	〃	$C_{10}H_{16}N_4 \cdot \frac{1}{2}H_2SO_4$	23.23	22.95
	47	217～218	needles	$C_{11}H_{18}ON_4 \cdot \frac{1}{2}H_2SO_4$	20.66	20.43
	72	206	〃	$C_{12}H_{20}ON_4 \cdot \frac{1}{2}H_2SO_4$	20.36	20.15
	73	190～192	plates	$C_{13}H_{22}ON_4 \cdot \frac{1}{2}H_2SO_4$	18.72	18.84
	98	227～228	prisms	$C_{11}H_{18}N_4 \cdot \frac{1}{2}H_2SO_4$	21.95	22.13
	65	200～202	〃	$C_{10}H_{16}N_4 \cdot \frac{1}{2}H_2SO_4$	20.24	20.30

These compounds synthesized were screened as to their various pharmacological activities. Among them, two compounds, 3-(*p*-toluidino)propylguanidine and 3-anilinopropylguanidine, showed stimulant effects. The pharmacological effect of these agents will be reported in a medical journal, in the near future.

Experimental

General Procedure for Synthesis of 2-Alkylaminopropionitrile——To a solution of 0.1 mole of amine in 30 ml. of EtOH, 0.1 mole of acrylonitrile in 30 ml. of EtOH was added with stirring at 15° during 20 min. The mixture was continued to stirring for 5 hr. at 15°, and then refluxed for 1 hr. After removal of the solvent, the resulting residue was distilled.

General Procedure for Synthesis of 3-Alkylaminopropylamine——A solution of 0.08 mole of 2-alkylaminopropionitrile in 30 ml. of dehyd. ether was added with stirring dropwise into the suspension of 4.4 g. of litium aluminum hydride in 200 ml. of dehyd. ether. The reaction mixture was refluxed with stirring for 3 hr. on a water bath and stirring was continued overnight at room temperature. To the mixture, 5 ml. of water, 5 ml. of 20% NaOH and 13 ml. of water were, in order, carefully added with stirring on cooling. Then, the mixture was filtered by suction and the filtrate was dried with Na_2SO_4. After removal of ether, the residue was distilled under reduced pressure.

General Procedure for Synthesis of 3-Arylaminopropylamine——A mixture of 0.1 mole of 3-bromopropylphthalimide and 0.2 mole of arylamine in 60 ml. of dehyd. xylene was refluxed with occasional shaking in

oil bath maintained at 120~130° for 10 hr. The mixture was filtered on warming and the solvent was removed by distillation. To the residue, 100 ml. of 95% EtOH and 5.9 g. of 85% hydrazine hydrate were added, and refluxed for 2 hr. on water bath. After cooling, the mixture was made strongly acid to Congo red paper with conc. HCl. The separated precipitates were filtered off and filtrate was concentrated under reduced pressure. The residue was added to a cold 40% NaOH with stirring. The resulting brown oil separated was extracted with $CHCl_3$ and the extrate was dried with Na_2SO_4. After removal of $CHCl_3$, the oily residue was distilled under reduced pressure.

General Procedure for Synthesis of 3-Substituted Aminopropylguanidine Sulfate——A solution of 0.06 mole of 3-substituted aminopropylamine and 0.06 mole of S-methyl isothiourea sulfate in 30 ml. of water was warmed on a water bath for 3~5 hr. until MeSH was finished to evolve. The mixture was concentrated and a suitable amount of Me_2CO was added. The resulting deposited crystals were colleted by suction and recrystallized from dil. EtOH or dil. MeOH. The compounds synthesized were illustrated in Table Ⅱ.

Experimental Method for the Test of Stimulant Effect——For this test, mice were employed. After the intraperitoneal injection of a compound to be tested, the symptoms were observed. If the compound produces the stimulating effect at doses no greater than 20 per cent of the LD_{50}, it was considered significant. As a reference standard compound, Amphetamine was used.

[Chem. Pharm. Bull. 15(2) 232~235 (1967)]

UDC 547.972.2.04

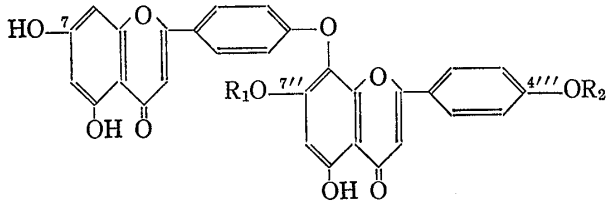
Hiroshi Miura and Nobusuke Kawano: The Partial Demethylation of Flavones. Ⅱ.*1 Formation of Isocryptomerin.

(*Faculty of Pharmaceutical Sciences, Nagasaki University**2)

Partial demethylation of cryptomerin B (Ⅱ) with hydrogen iodide formed a new compound, isocryptomerin (Ⅲ).

(Received May 13, 1966)

Cryptomerin A (I) and B (Ⅱ) were reported[1] as the first examples of naturally occurring hinokiflavone methyl ethers. In the course of their structural studies one of two methoxyl groups in cryptomerin B (Ⅱ) was considerably resistant to demethylation with hydrogen iodide,*3 whereas cryptomerin A (I) was easily demethylated to hinokiflavone. We now report the formation of isocryptomerin (Ⅲ), a new compound and an isomer of cryptomerin A by partial demethylation of cryptomerin B.



I : R_1=H, R_2=CH_3
Ⅱ : R_1=R_2=CH_3
Ⅲ : R_1=CH_3, R_2=H

In the preceeding paper[2] of this series genkwanin (7-O-methyl apigenin) was reported to be prepared from apigenin trimethyl ether by demethylation under a mild condition. However, as isocryptomerin is more stable against hydrogen iodide than genkwanin it is comparatively easy obtainable in satisfactory yield as pale yellow

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*1 Part I. This Bulletin, **14**, 299 (1966).

*2 4-23 Bunkyo-cho, Nagasaki (三浦博史, 河野信助).

*3 Prolonged reaction time and a large amount of reagent allowed a correct value in a Zeisel methoxyl determination.

1) H. Miura, N. Kawano, A.C. Waiss, Jr.: This Bulletin, **14**, 1404 (1966).

2) N. Kawano, H. Miura, E. Matsuishi: *Ibid.*, **14**, 299 (1966).