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Studies on Azetidine Derivatives. I. Synthesis of 3-Substituted Azetidine Derivatives[1]

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In order to find pharmacologically active azetidine derivatives, convenient procedures for the synthesis of 3-substituted azetidines have been investigated. 3-Azetidinyl mesylates (IV), prepared by treatment of azetidin-3-ols (I) with sulfenes, were shown to be useful intermediates for the synthesis of 3-substituted azetidines, 3-amino-, 3-cyano-, 3-guanidinoazetidines (V, VI and VIII) and azetidine-3-carboxylic acids (VII) *via* VI. 1-Cyclohexyl-3-guanidinoazetidine showed an excellent antihypertensive activity.

Recently, considerable investigations have been reported on the synthesis of azetidine derivatives.[3] On the other hand, naturally occurring antibiotics like penicillins and cephalosporins contain the azetidin-2-one moiety as part of their structures. Other naturally occurring azetidine-2-carboxylic acid[4] and the presence of 3-ethylideneazetidine-2-carboxylic acid, polyoximic acid, in some of antibiotics polyoxins[5] have also been reported. But only a few attempts have been made to synthesize azetidines for the development of new drugs.[3,6] This appears to be due to the lack of simple and convenient methods for preparation of azetidine derivatives and introduction of substituents onto the azetidine ring. In the course of our synthetic programs of azetidine derivatives to find pharmacologically active substances,[7] various azetidine derivatives have been synthesized and some of them have been reported.[8] In the present paper, we will report preparation of some azetidin-3-ols and 3-substituted azetidines obtained by the nucleophilic substitution of 3-azetidinyl mesylates.

Preparation of 1-Substituted Azetidin-3-ols (I)

Gaertner reported an elegant synthesis of 1-substituted azetidin-3-ols (I).[9] But, this procedure suffers two disadvantages: first, a long period of the reaction time (3—12 days) is required for the completion of the reaction, and second, the azetidinols substituted by non-bulky alkyl groups at the 1-position can not be prepared and, therefore, the reaction is not feasible for the synthesis of 1-α-methylphenethylazetidin-3-ol (Ii) (Table I).

In the present investigation, it was found that 1-alkylamino-3-chloro-2-propanols[9] were heated under reflux in acetonitrile for 4—5 hr to afford 1-alkylazetidin-3-ols (I) as the hydro-

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[1] Presented at the Annual Meeting of the Pharmaceutical Society of Japan, Fukuoka, April, 1971; T. Okutani, Jap. Patent 7213500 (1968); T. Okutani and A. Nagaoka, Jap. Patent 7247382 (1969).

[2] Location: *Juso-Nishinocho, Higashiyodogawa-ku, Osaka.*

[3] Review: K. Masuda, *Yuki Gosei Kagaku Kyokai Shi*, **30**, 271 (1972).

[4] L. Fowden and M.H. Richard, *Biochem. Biophys. Acta*, **71**, 459 (1963); E.J. Hewitt and B.A. Notton, *Phytochemistry*, **6**, 1329 (1967); D.J. Cummings, V.A. Chapman, S.S. Delong, and L. Mondale, *J. Virol.*, **1**, 193 (1967).

[5] K. Isono, K. Asahi, and S. Suzuki, *J. Am. Chem. Soc.*, **91**, 7490 (1969).

[6] *a*) E. Testa, A. Wittigens, G. Maggie, and G. Bianchi, "Research Progress in Organic-Biological and Medicinal Chemistry," Vol. 1, ed. by U. Gallo and L. Santamaria, North-Holland Publisher, Co., Amsterdam, 1964, pp. 477—583; *b*) E. Bellasio and G. Cristiani, *J. Med. Chem.*, **12**, 196 (1969); *c*) D.D. Miller, J. Fowble, and P.N. Patil, *J. Med. Chem.*, **16**, 177 (1973).

[7] K. Masuda, T. Okutani, A. Morimoto, T. Kaneko, K. Kikuchi, T. Hirata, Y. Tajima, T. Jimpu, and A. Nagaoka, *J. Takeda Research Lab.*, **31**, 453 (1972).

[8] A. Morimoto, T. Okutani, and K. Masuda, *Chem. Pharm. Bull.* (Tokyo), **21**, 228 (1973).

[9] *a*) V.R. Gaertner, *Tetrahedron Letters*, **1966**, 4691; *b*) *Idem.*, *J. Org. Chem.*, **32**, 2972 (1967).

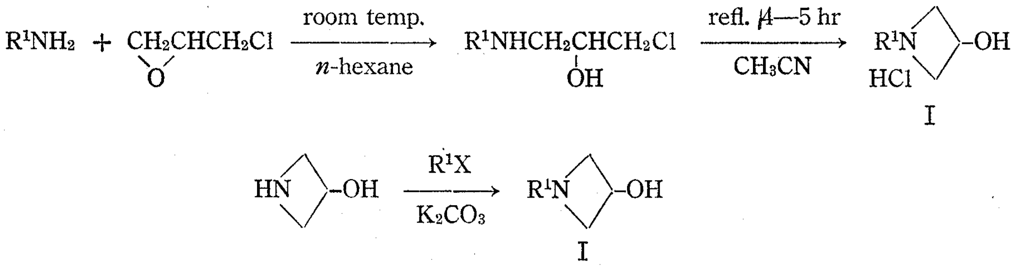

Chart 1

chloride in good yields (Table I), from which free bases (I) were obtained easily by the usual manner. 1-Ethyl and 1-α-methylphenethylazetidin-3-ols (Ia and Ii) were prepared by the direct alkylation of 1-unsubstituted azetidin-3-ol[10] with ethyl iodide and α-methylphenethyl tosylate, respectively.

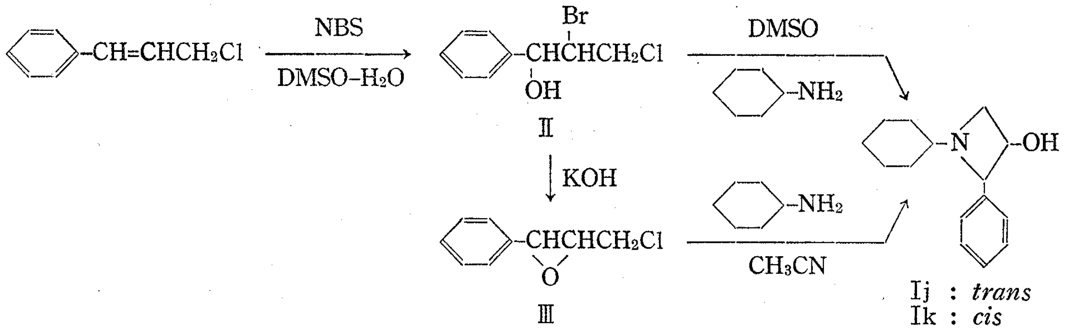

Chart 2

As for 1,2-disubstituted azetidin-3-ols, only *trans*- and *cis*-1-*t*-butyl-2-methylazetidin-3-ols have so far been reported.[9b,11] In our case, 2-bromo-3-chloro-1-hydroxy-1-phenylpropane (II) was treated with two mole equivalents of cyclohexylamine in dimethyl sulfoxide (DMSO) for 20 hr at 50—60° to afford *trans*-1-cyclohexyl-2-phenylazetidin-3-ol (Ij) and the *cis*-isomer (Ik) in 52% and 4% yields, respectively. While 3-chloro-1,2-epoxy-1-phenylpropane (III) prepared from II underwent reaction with an equimolar amount of cyclohexylamine in acetonitrile under reflux for 8 hr to give Ij and Ik in 13% and 10% yields, respectively. Stereochemistry of these isomers has been established by chemical evidence[12] and nuclear magnetic resonance (NMR) studies with a shift reagent.[13]

Preparation and Reactions of 1-Substituted 3-Azetidinyl Mesylates (IV)

Recently various 3-substituted 1-*t*-butylazetidines have been synthesized by the reactions of the corresponding tosylate[14] and chloride[15] with nucleophilic reagents. However, these reactions do not appear satisfactory because of undesired side reactions such as ring opening and ring contraction during the tosylation[14a] and chlorination reactions[15] respectively, and also for poor yields. Ring opening due to the attack of tosyl chloride at the ring nitrogen

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[10] S.S. Chatterjee and D.J. Triggle, *Chem. Commun.*, **1968**, 93.

[11] R.H. Higgins and N.H. Cromwell, *J. Heterocyclic Chem.*, **8**, 1059 (1971).

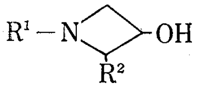
[12] T. Okutani and K. Masuda, *Chem. Pharm. Bull.* (Tokyo), **22**, 1498 (1974).

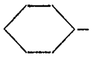
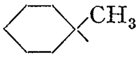
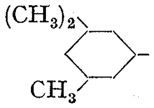
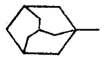
[13] T. Okutani, A. Morimoto, T. Kaneko, and K. Masuda, *Tetrahedron Letters*, **1971**, 1115.

[14] *a*) T. Chen, T. Sanjiki, H. Kato, and M. Ohta, *Bull. Chem. Soc. Japan*, **40**, 2401 (1967); *b*) T. Chen, H. Kato, and M. Ohta, *ibid.*, **41**, 712 (1968); *c*) J.A. Deyrup and C.L. Moyer, *Tetrahedron Letters*, **1968**, 6179; R.H. Higgins, F.M. Behlem, D.F. Eggli, J.H. Kreymborg, and N.H. Cromwell, *J. Org. Chem.*, **37**, 524 (1972); R.H. Higgins and N.H. Cromwell, *ibid.*, **37**, 2918 (1972).

[15] V.R. Gaertner, *Tetrahedron Letters*, **1968**, 5919; *idem.*, *J. Org. Chem.*, **35**, 3952 (1970).

TABLE I. 1-Substituted Azetidin-3-ols (I)



Compd. No.	R¹	R²	Method	mp (bp) (°C)	Yield (%)	Formula	Analysis (%) Found (Calcd.) C	H	N
a	C_2H_5	H	C	40—42 (1.0 mmHg)	6	$C_5H_{11}ON$	59.21 (59.36)	10.85 (10.96)	13.54 (13.84)
b	iso-C_3H_7	H	B A	140—141[a,b]	66 6[c]	$C_6H_{14}ONCl$	47.55 (47.52)	9.38 (9.30)	9.19 (9.23)
c	*t*-C_4H_9	H	B A	165—166[a,d]	55 47	$C_7H_{16}ONCl$	50.45 (50.75)	9.60 (9.74)	8.50 (8.46)
d		H	B A	159—160[a,e]	75[f] 45[f]	$C_9H_{18}ONCl$	56.13 (56.39)	9.60 (9.46)	7.45 (7.31)
e		H	A	92—98 (0.4 mmHg)	55	$C_{10}H_{19}ON$	70.94 (70.96)	11.41 (11.31)	7.99 (8.28)
f		H	A	96—98 (0.3—0.6mmHg)	36	$C_{12}H_{23}ON$	72.71 (73.04)	11.72 (11.75)	6.80 (7.10)
g		H	A	171—172	49	$C_{13}H_{21}ON$	74.99 (75.31)	10.36 (10.21)	6.86 (6.76)
h	$C_6H_5CH(CH_3)$	H	B A	44—49[g]	45 24	$C_{11}H_{15}ON$	74.10 (74.54)	8.53 (8.65)	7.90 (8.02)
i	$C_6H_5CH_2CH(CH_3)$	H	C A	83—84.5[h]	60 9	$C_{12}H_{17}ON$	75.28 (75.34)	8.79 (8.96)	7.35 (7.32)

a) HCl salt *b*) free base: mp 56—57° (lit.[8] mp 57—58°) *c*) ref. 8 *d*) free base: mp 45—47° (lit.[8] mp 44—46°) *e*) free base: mp 79—80° (lit.[8] mp 79—80°) *f*) yield from 1-cyclohexylamino-3-chloro-2-hydroxypropane *g*) bp 110°/0.3 mmHg *h*) bp 107—110°/0.07 mmHg (lit. bp 118—120°/0.1 mmHg; Neth. Patent 6906892) (1970)

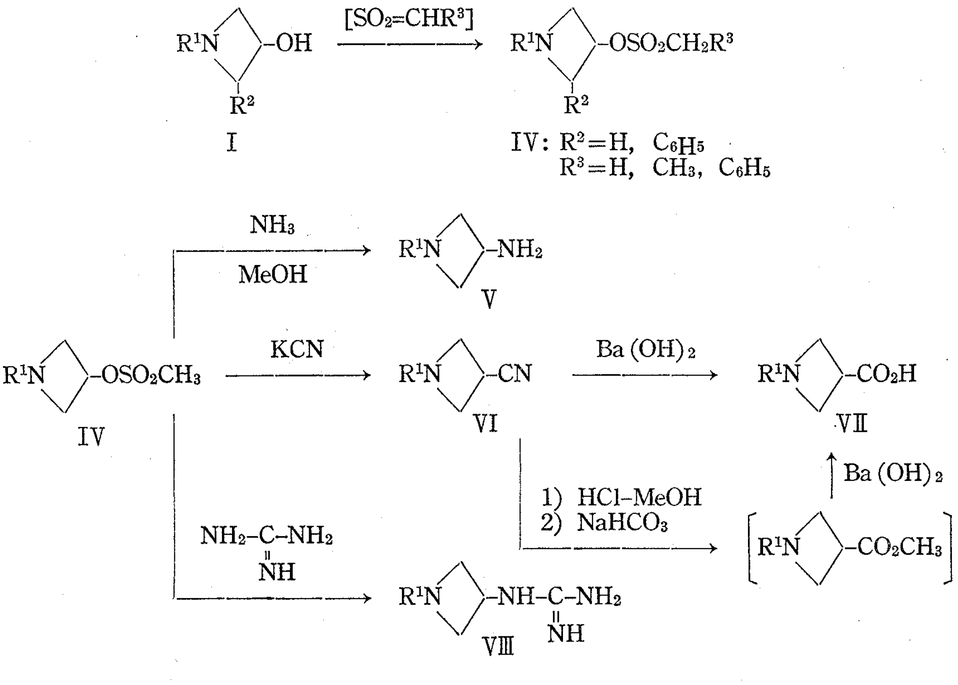


Chart 3

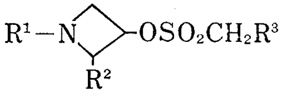
appears to be inevitable in the tosylation of azetidinols (I) except for I with a bulky alkyl substituent at the 1-position.[14a,16]

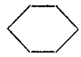
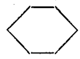
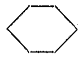
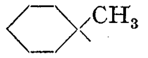
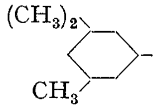
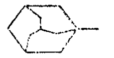
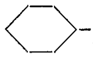
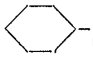
We expected that treatment of I with sulfenes[17] would minimize these side reactions and afford 1-substituted 3-azetidinyl mesylates (IV), and that these mesylates could serve as intermediate for the synthesis of various azetidine derivatives.[16]

Thus, treatment of I with mesyl chloride in the presence of equimolar amount of triethylamine in dry benzene under ice-cooling gave corresponding mesylates (IV) in excellent yields (Table II). The mesylates (IV) formed in the reaction mixture were usually isolated as their salts and these salts can be stored in crystalline forms; otherwise, they are unstable in an oily state and changed to resinous materials, even when stored in a refrigerator.

Various 3-substituted azetidines were easily prepared by the reactions of IV with nucleophilic reagents.[14] Treatment of IV with methanolic ammonia for a few days at room tem-

TABLE II. 1-Substituted 3-Alkylsulfonyloxyazetidines (IV)



Compd. No.	R^1	R^2	R^3	mp (°C)	Yield (%)	Formula	Analysis (%) Found (Calcd.) C	H	N
a	C_2H_5	H	H	142—143[a]	61	$C_8H_{15}O_7NS$	35.64 (35.68)	5.61 (5.62)	5.09 (5.20)
b	iso-C_3H_7	H	H	166—168[a]	88	$C_9H_{17}O_7NS$	38.21 (38.15)	6.04 (6.05)	4.70 (4.94)
c	*t*-C_4H_9	H	H	146—148[a,b]	75	$C_{10}H_{19}O_7NS$	40.42 (40.39)	6.41 (6.44)	4.70 (4.71)
d	*t*-C_8H_{17}	H	H	126[a]	75	$C_{14}H_{27}O_7NS$	47.49 (47.56)	7.60 (7.70)	3.69 (3.96)
e		H	H	156—157[a,c]	85	$C_{12}H_{21}O_7NS$	44.58 (44.57)	6.47 (6.55)	4.35 (4.33)
f		H	CH_3	143—144.5[a]	32	$C_{13}H_{23}O_7NS$	46.33 (46.28)	7.17 (6.87)	4.32 (4.15)
g		H	C_6H_5	159—160[a,b]	73	$C_{18}H_{25}O_7NS$	53.97 (54.12)	6.32 (6.31)	4.15 (3.71)
h		H	H	139—140[a]	88	$C_{13}H_{23}O_7NS$	46.33 (46.28)	6.73 (6.87)	4.05 (4.15)
i		H	H	141—142[a]	97	$C_{15}H_{27}O_7NS$	49.59 (49.30)	7.58 (7.45)	3.57 (3.83)
j		H	H	92—93[e]	81	$C_{14}H_{23}O_3NS$	59.09 (58.92)	8.13 (8.12)	4.59 (4.91)
k	$C_6H_5CH(CH_3)$	H	H	93—94.5[a,f]	94	$C_{14}H_{19}O_7NS$	48.81 (48.68)	5.49 (5.54)	4.15 (4.06)
l	$(C_6H_5)_2CH$	H	H	114.5—116.5[g]	74	$C_{17}H_{19}O_7NS$	64.28 (64.38)	6.15 (6.03)	4.30 (4.14)
m	 (*trans*)	C_6H_5	H	84—85	93	$C_{16}H_{23}O_3NS$	62.40 (62.11)	7.55 (7.49)	4.29 (4.53)
n	 (*cis*)	C_6H_5	H	100—101	81	$C_{16}H_{23}O_3NS$	62.32 (62.11)	7.52 (7.49)	4.42 (4.53)

a) hydrogen oxalate *b*) HCl salt: mp 123° *c*) HCl salt: mp 123—124°; free base: mp 43.5—45° *d*) free base: mp 90—91° *e*) HCl salt: mp 141° *f*) HCl salt: mp 123—124° *g*) rit.[17] mp 113—114°

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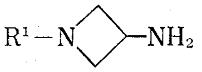
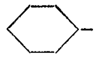
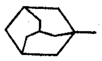
16) Very recently, preparation and reactions of 1-diphenylmethyl-3-azetidinyl mesylate have been reported; A.G. Anderson, Jr. and R. Lok, *J. Org. Chem.*, 37, 3953 (1972).

17) W.E. Truce and L.K. Liu, "Mechanisms of Reactions of Sulfur Compound," Vol. 4, ed. by N. Karasch, Inter-Science Research Foundation, Santa Monica, California, 1969, pp. 145—154.

TABLE III. 1-Substituted 3-Aminoazetidines (V)

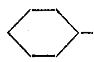
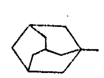


Compd.	R^1	mp (bp) (°C)	Yield (%)	Formula	Analysis (%) Found (Calcd.)		
					C	H	N
a	iso-C_3H_7	100—102[a]	36	$C_7H_{18}O_3N_2S$	51.55 (51.80)	11.23 (11.17)	17.03 (17.26)
b	*t*-C_4H_9	58—59[b] (13 mmHg)	43	$C_7H_{16}N_2$	— —	— —	— —
c	*t*-C_8H_{17}	109—110[a]	68	$C_{12}H_{28}O_3N_2S$	51.38 (51.39)	10.35 (10.06)	9.83 (9.98)
d		134—137[a,b]	88	$C_{10}H_{22}O_3N_2S$	48.11 (47.99)	8.83 (8.85)	11.25 (11.18)
e	$C_6H_5CH(CH_3)$	187—189[a]	55	$C_{13}H_{20}O_3N_2S$	52.92 (52.91)	7.44 (7.40)	10.25 (10.28)
f		285—289[a,c]	73	$C_{14}H_{26}O_3N_2S$	55.56 (55.59)	8.72 (8.66)	9.11 (9.26)

a) methanesulfonic acid salt b) rit.[14b] bp 55—61°/13.5 mmHg c) HCl salt: mp 263—265° d) free base: mp 61—63° (from pet. ether)

perature gave 1-substituted 3-aminoazetidines (V) as the methanesulfonic acid salt (Table III). 1-Substituted 3-cyanoazetidines (VI) were obtained by the treatment of IV with potassium cyanide in methanol (Table IV). Hydrolysis of VI with barium hydroxide afforded 1-substituted azetidine-3-carboxylic acids (VII) except for 1-diphenylmethyl and 1-adamantyl-3-cyanoazetidines (VIe and VIf) which gave only trace amounts of the corresponding acids, while treatment of VI with methanolic hydrogen chloride at room temperature, followed by the neutralization with aqueous sodium bicarbonate yielded the corresponding methyl esters, which were easily hydrolyzed with barium hydroxide to give the carboxylic acids (VIIe and VIIf) in excellent yields (Table V).

TABLE IV. 1-Substituted 3-Cyanoazetidines (VI)

Compd.	R^1	mp (bp) (°C)	Yield (%)	Formula	Analysis (%) Found (Calcd.)		
					C	H	N
a	*t*-C_4H_9	60—61[a] (2 mmHg)	79	$C_8H_{14}N_2$	69.55 (69.52)	10.48 (10.20)	19.92 (20.26)
b	*t*-C_8H_{17}	[b]	83[c]	$C_{12}H_{22}N_2$	— —	— —	— —
c		83.5—85	67	$C_{10}H_{16}N_2$	72.84 (73.12)	9.68 (9.82)	17.18 (17.06)
d	$C_6H_5CH(CH_3)$	100—107 (0.3 mmHg)	61	$C_{12}H_{14}N_2$	77.33 (77.37)	7.45 (7.58)	15.60 (15.58)
e	$(C_6H_5)_2CH$	150—151[b]	59	$C_{17}H_{16}N_2$	82.23 (82.22)	6.58 (6.50)	11.01 (11.28)
f		94—95	70	$C_{14}H_{20}N_2$	77.49 (77.73)	9.18 (9.31)	12.64 (12.94)

a) rit.[14] 39—40.5°/1.5 mmHg b) not distilled c) crude yield d) rit.[17] 152—153°

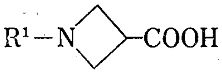
These results indicate that 3-azetidinyl methylates (IV) prepared from azetidinols (I) are useful intermediates for the synthesis of various azetidine derivatives.

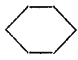
Reactions of diastereomeric mesylates (IVm and IVn) will be reported in the following paper.[12)]

1-Substituted 3-Guanidinoazetidines (VIII)

It has been well documented that a series of guanidino compounds exemplified by Guanethidine, 2-(octahydro-1-azocynyl)ethyl guanidine, show excellent antihypertensive activities.

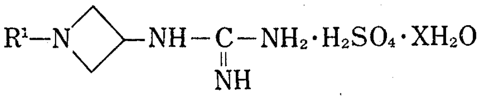
Table V. 1-Substituted Azetidine-3-carboxylic Acids (VII)

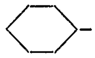
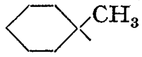
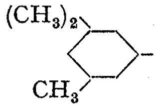


Compd.	R¹	mp	Yield	Formula	Analysis (%) Found (Calcd.)		
					C	H	N
a	t-C_4H_9	189—190[a)]	50	$C_8H_{15}O_2N\cdot H_2O$	54.78 (54.83)	9.88 (9.78)	7.75 (7.99)
b	t-C_8H_{17}	170—172	61	$C_{12}H_{23}O_2N\cdot H_2O$	62.11 (62.30)	11.13 (10.89)	5.89 (6.05)
c		161—163	87	$C_{10}H_{17}O_2N\cdot H_2O$	59.49 (59.68)	9.78 (9.51)	6.71 (6.91)
d	$C_6H_5CH(CH_3)$	166—167	57	$C_{12}H_{15}O_2N\cdot H_2O$	64.28 (64.55)	7.89 (7.67)	5.98 (6.27)
e	$(C_6H_5)_2CH$	192—195[b)]	89[c)]	$C_{17}H_{17}O_2N$	76.55 (76.37)	6.58 (6.41)	4.99 (5.23)
f		190—192[d)]	96[e)]	$C_{14}H_{21}O_2N$	71.43 (71.45)	9.15 (8.99)	5.80 (5.95)

a) lit.[14)] mp 189—191° b) lit.[17)] mp 198° c) Yield from the methyl ester, mp 67—68° (from pet. ether), which was obtained from VIe in 98% yield. d) decomposition e) Yield from the methyl ester, liquid, which was obtained from VIf in 93% yield.

Table VI. 1-Substituted 3-Guanidinoazetidines (VIII)



Compd. No.	R¹	X	mp[a)] (°C)	Yield (%)	Formula	Analysis (%) Found (Calcd.)			
						C	H	N	S
a	t-C_4H_9	0	240—241	54	$C_8H_{20}O_4N_4S$	35.70 (35.81)	7.56 (7.51)	20.90 (20.88)	12.04 (11.95)
b	t-C_8H_{17}	0	246—247	19	$C_{12}H_{28}O_4N_4S$	43.99 (44.42)	8.74 (8.70)	17.14 (17.27)	9.70 (9.88)
c		2	204—205	44	$C_{10}H_{22}O_6N_4S$	36.49 (36.35)	7.63 (7.93)	17.21 (16.96)	9.71 (9.70)
d		0	218—220	6	$C_{11}H_{24}O_5N_4S$	42.50 (42.84)	7.89 (7.84)	18.01 (18.17)	— —
e		1	216—217	20	$C_{13}H_{30}O_5N_4S$	42.18 (41.90)	8.07 (8.09)	15.20 (15.03)	8.53 (8.06)
f	$C_6H_5CH(CH_3)$	2	190—191	39	$C_{12}H_{22}O_6N_4S$	40.48 (40.66)	6.57 (6.83)	15.83 (15.81)	9.29 (9.05)
g	$(C_6H_5)_2CH$	0	173	36	$C_{17}H_{22}O_5N_4S$	56.61 (56.70)	5.63 (5.51)	14.20 (13.92)	— —

a) decomposition

Recently, synthesis of 1-(β-guanidinoethyl)- and 1-guanyl-azetidines has been reported but these azetidines failed to show antihypertensive activities.[4b] In attempt to find antihypertensive agents, preparation of 1-substituted 3-guanidinoazetidines (VIII) has been investigated. As for preparation of guanidino compounds, it was reported that the reaction of a tosylate with an equivalent quantity of guanidine afforded a guanidino compound as the *p*-toluenesulfonic acid ester.[18]

In the present case, two equivalents of guanidine were required for the completion of the reaction. Treatment of the mesylate (IV) with two equivalents of guanidine in isopropanol at room temperature afforded the corresponding guanidinoazetidines (VIII), which were isolated as the sulfates (Table VI).

Among these compounds, 1-cyclohexyl-3-guanidinoazetidine (VIIIc) showed an excellent antihypertensive activity as potent as that of Guanethidine.[19]

Experimental

All melting points were recorded on a micro hot stage apparatus and are uncorrected. NMR spectra were recorded on a Varian Model HA-100 spectrophotometer using TMS as internal standard. Infrared (IR) spectra were recorded on a Hitachi Model 215 spectrophotometer.

Procedures for the Preparation of 1-Substituted Azetidin-3-ols (I)——Method A: *t*-Butyl, cyclohexyl, 1-methylcyclohexyl, 3,3,5-trimethylcyclohexyl, adamantyl, α-methylbenzyl, α-methylphenethyl and diphenyl[10,16] azetidinols (I) were prepared according to the literature.[9]

Method B: a) A primary amine (0.5 mole) and epichlorohydrin (0.5 mole) were dissolved in *n*-hexane (350 ml) under ice-cooling and the mixture was allowed to stand at room temperature for 2 days. After evaporation of the solvent under reduced pressure at room temperature, the residue was dissolved in acetonitrile (350 ml) and heated under reflux for 5 hr. After evaporation of the solvent, the precipitate was collected and washed with $(C_2H_5)_2O$ to give I as the HCl salt, which was recrystallized from MeOH–$(C_2H_5)_2O$. In the case of Ih, the HCl salt was not crystallized and an oily residue was treated with an aqueous alkali and extracted with $(C_2H_5)_2O$. After evaporation of the solvent, an oily residue was submitted to distillation to yield Ih.

b) 1-Cyclohexylamino-3-chloro-2-hydroxypropane[9] (15 g), mp 76—78° (from *n*-hexane), prepared according to the procedure described in a), was dissolved in acetonitrile (75 ml) and the solution was heated under reflux for 4 hr. A part of the solvent was evaporated under reduced pressure and the residue was chilled to afford the precipitate, which was collected by filtration to give 10.2 g of Id as the HCl salt. The salt was recrystallized from MeOH–$(C_2H_5)_2O$. The salts prepared by Method A and B gave easily the corresponding free bases by neutralization with an aqueous alkali, followed by extraction with $(C_2H_5)_2O$.

Method C: a) To a solution of isopropanol (50 ml), in which was dissolved Na (1.15 g), was added 1-unsubstituted azetidinol HCl[10] (8 g) and the solution was filtered. To the solution were added K_2CO_3 (10.5 g) and ethyl iodide (11.4 g) and the mixture was heated under reflux for 3 hr. After filtration of the precipitate, the filtrate was evaporated and the oily residue was submitted to distillation to yield 0.45 g of Ia.

b) A mixture of 1-unsubstituted azetidinol HCl[10] (2 g), 2-phenyl-1-methylethyl tosylate (5.4 g) and K_2CO_3 (3.9 g) was heated under reflux for 24 hr and the mixture was filtered. After evaporation of the solvent *in vacuo*, the residue to which water was added was extracted with $(C_2H_5)_2O$ and the organic layer was dried over $MgSO_4$. To the solution was added 10% ethereal oxalic acid solution and the organic solvent was removed by decantation. The remaining resinous substance was dissolved in a saturated Na_2CO_3 solution and extracted with $(C_2H_5)_2O$. After the organic layer was dried over $MgSO_4$, evaporation of the solvent afforded crude crystals, which were recrystallized from pet. ether to give Ii (2.1 g).

2-Bromo-3-chloro-1-hydroxy-1-phenylpropane (II)——To a stirred solution of *trans*-cinnamyl chloride (60.8 g) and water (8 g) in DMSO (70 ml), was added[18] N-bromosuccinimide (NBS) (71.2 g) under ice-cooling in nitrogen atmosphere for a period of 30 min and then the mixture was stirred under the same conditions for additional 30 min. The reaction mixture was extracted with $(C_2H_5)_2O$ and the organic layer was washed with a saturated Na_2CO_3 solution and finally with water. After the organic layer was dried over $MgSO_4$, evaporation of the solvent gave an oily residue, which was submitted to distillation to yield II (81 g, 81%), bp 121—124° (0.6—1.0 mmHg), light yellow oil. *Anal.* Calcd. for $C_9H_{10}OBrCl$: C, 43.14; H, 4.02. Found: C, 43.46; H, 3.78.

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18) A.M. Monro, *Chem. Ind.* (London), **1964**, 1806.

19) N. Toda, H. Usui, and K. Shimamoto, *Japan J. Pharm.*, 22, 125 (1972); K. Kikuchi, Y. Maki, Y. Tajima, T. Jimpu, A. Nagaoka, M. Hirata, and K. Kawazoe, *J. Takeda Research Lab.*, **30**, 711 (1971).

3-Chloro-1,2-epoxy-1-phenylpropane (III)——To $(C_2H_5)_2O$ (100 ml) was added powdered KOH (8.5 g) and II (34 g), and the mixture was stirred at room temperature overnight. The organic layer was separated by decantation. After evaporation of the solvent, an oily residue was obtained, which was submitted to distillation to yield III (15.6 g, 68%), bp 83—85° (0.5—0.6 mmHg). *Anal.* Calcd. for C_9H_9OCl: C, 64.11; H, 4.62. Found: C, 63.85; H, 4.51.

***trans*- and *cis*-1-Cyclohexyl-2-phenylazetidin-3-ols (Ij and Ik)**——a) Cyclohexylamine (4 g) and II (5 g) were dissolved in DMSO (50 ml) and the mixture was allowed to stand at room temperature overnight. Then, the mixture was heated at 50—60° for 12 hr and poured into aq. 2N NaOH, and extracted with $(C_2H_5)_2O$. The organic layer was dried over $MgSO_4$ and evaporated to dryness. To the oily residue was added pet. ether and the precipitate was collected and washed with pet. ether to give crude crystals. Recrystallization from pet. ether gave Ij (2.4 g, 52%), mp 138—140°. *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.89; H, 9.31; N, 6.10. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3160 (OH). NMR (100 MHz, $CDCl_3$) δ ppm: *ca.* 0.60—2.30 (11H, m, cyclohexyl proton), 2.40 (1H, s, OH), 2.65 (1H, t, azetidine ring proton), 3.67 (1H, t, azetidine ring proton), 3.71 (1H, d, azetidine ring proton), 3.99 (1H, q, azetidine ring proton), 7.20—7.50 (5H, m, phenyl proton). The filtrate was concentrated *in vacuo*, and to the oily residue was added a small amount of pet. ether and the precipitate formed was collected to give crude crystals, which were recrystallized from pet. ether to yield Ik (0.52 g, 4%), mp 101—102.5°. *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found: C, 77.92; H, 9.00; N, 6.13. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 3060 (OH). NMR (100 MHz, $CDCl_3$) δ ppm: *ca.* 0.70—2.40 (11H, m, cyclohexyl proton), 3.11 (1H, q, azetidine ring proton), 3.15 (1H, d of t, azetidine ring proton), 4.13 (1H, d, azetidine ring proton), 4.19 (1H, t, azetidine ring proton), 7.10—7.45 (5H, m, phenyl proton).

b) A solution of III (4.6 g) and cyclohexylamine (2.75 g) in acetonitrile (23 ml) was heated under reflux for 8 hr. The precipitate was filtered off and the filtrate was concentrated under reduced pressure to give an oily residue, which was treated as described in a) to yield Ij (0.8 g, 13%) and Ik (0.65 g, 10%).

General Procedure for the Preparation of 1-Substituted 3-Alkylsulfonyloxyazetidines (IV)——To a stirred solution of I (0.054 mole) and triethylamine (0.054 mole) in dry benzene (120 ml), was added alkylsulfonyl chloride (0.054 mole) dropwise under ice-cooling and with rigorous exclusion of moisture over a period of 20 min, and the mixture was stirred at room temperature for additional 3 hr. The precipitate formed was collected by filtration. To the filtrate was added 10% ethereal oxalic acid solution (or introduced dry hydrogen chloride under ice-cooling) to give crude crystals, which were recrystallized from EtOH–$(C_2H_5)_2O$ to yield IV as the hydrogen oxalate (or the HCl salt). In the cases of Ij and Ik, the oxalates were not crystallized and, therefore, to the resinous substances was added a saturated $NaHCO_3$ solution and extracted with $(C_2H_5)_2O$. After being dried over $MgSO_4$, the organic solvent was evaporated at room temperature to give crude crystals, which were recrystallized from pet. ether.

General Procedure for the Preparation of 1-Substituted 3-Aminoazetidines (V)——To 10% methanolic ammonia solution (5 ml) was added IV (1 mmole) and the mixture was allowed to stand at room temperature for a few days. After evaporation of the solvent, to the residue was added AcOEt and crude crystals were collected. Recrystallization of the crystals from iso-PrOH–$(C_2H_5)_2O$ gave V as methanesulfonic acid salts.

General Procedure for the Preparation of 1-Substituted 3-Cyanoazetidines (VI)——The nitriles (VI) were prepared according to the literature described by Chen, *et al.*[14a)] VIe and VIf were recrystallized from *n*-hexane.

General Procedure for the Preparation of 1-Substituted Azetidine-3-carboxylic Acids (VII)——To 10% methanolic hydrogen chloride (20 ml) was added VI (1 mmole) and the mixture was allowed to stand at room temperature for a few days. After evaporation of the solvent under reduced pressure at room temperature, the residue to which a saturated $NaHCO_3$ solution was added was extracted with $(C_2H_5)_2O$ and the organic layer was dried over $MgSO_4$. Evaporation of the solvent afforded the methyl ester, which was added to a solution of $Ba(OH)_2 \cdot 8H_2O$ (500 mg) in 5% aq. dioxane (10 ml). The mixture was heated under reflux for 30 min and cooled to room temperature. After addition of water (200 ml), carbon dioxide was introduced to the solution and the precipitate was filtered off. After evaporation of the solvent, $CHCl_3$ was added to the residue and the $CHCl_3$ solution was heated and filtered. Evaporation of the solvent gave crude crystals, which were recrystallized from EtOH–$(C_2H_5)_2O$ or $CHCl_3$ to yield VII. VIIa, VIIb, VIIc and VIId were prepared according to the procedure described by Chen, *et al.*[14a)]

General Procedure for the Preparation of 1-Substituted 3-Guanidinoazetidines (VIII)——To a solution of isopropanol (30 ml), in which was dissolved Na (19.5 mmoles), was added guanidine hydrochloride (19.5 mmoles) and the mixture was heated under reflux for 30 min. After the precipitate was filtreed off, IV (9.7 mmoles) in isopropanol (20 ml) was added to the resulting solution and the mixture was allowed to stand at room temperature overnight. After heated at 40—50° for 30 min, the reaction mixture was cooled under ice-cooling and the precipitate was collected by filtration. To the filtrate was added dropwise conc. H_2SO_4 (9.7 mmoles) under ice-cooling and the precipitate formed was collected by filtration. Recrystallization from EtOH–water gave VIII as the sulfate.

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