Notes

[Chem. Pharm. Bull. 19(11)2404—2409(1971)]

UDC 547.787.1.057 : 547.717.04

Reaction of Epoxides. II.[1] Synthesis of Oxazolidine by the Reaction of Epoxide with Schiff Base

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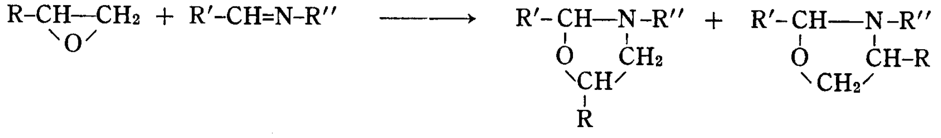
(Received February 15, 1971)

Oda, *et al.*[3] have reported that aliphatic epoxides reacted with aliphatic and aromatic nitriles to form 2,4-disubstituted oxazolines and isomeric 2,5-disubstituted oxazolines. They[4] have also found that oxazolidines were formed by the cyclic addition of a few simple epoxides to Schiff base in the presence of Lewis acid catalyst. As illustrated by the following equation, two isomeric adducts would be possible to form, though no 2,3,4-trisubstituted isomer was obtained.



We have now attempted to extend this addition for the general synthesis of oxazolidines and to obtain the isomeric products. This paper is concerned with the reaction of 2,3-epoxypropyl ether and 2,3-epoxypropyl thioether with Schiff base.

In order to obtain 2,3-epoxypropyl alkyl or aryl ether and 2,3-epoxypropyl alkyl or aryl thioether, several alcohols, phenols and thiols were attempted to react with epichlorohydrine (Chart 1).

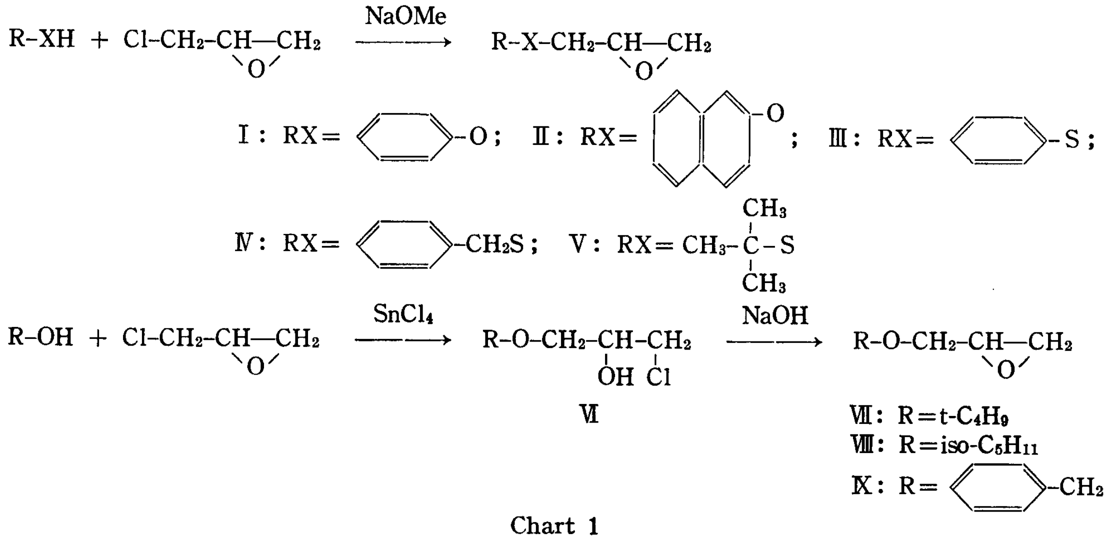


Chart 1

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[1] Part I: S. Hayashi, M. Furukawa, Y. Fujino, T. Nakao, and K. Nagato, *Chem. Pharm. Bull.* (Tokyo), **19**, 1594, (1971).

[2] Location: *a*) *Oe-moto-machi, Kumamoto*; *b*) *Yoshitomi-cho, Fukuoka.*

[3] R. Oda, M. Okano, S. Tokiura and F. Misumi, *Bull. Chem. Soc. Japan*, **35**, 1219 (1962).

[4] R. Oda, M. Okano, S. Tokiura and A. Miyano, *Bull. Chem. Soc. Japan*, **35**, 1216 (1962).

Phenols and thiols, such as phenol,[5,6] β-naphthol, thiophenol, benzylthiol and *t*-butylthiol, reacted easily with epichlorohydrine to give the corresponding epoxides (I—V) in fairly good yields. When alcohols were allowed to react with epichlorohydrine under the similar condition, however, extremely low yields of the products were obtained, probably because epichlorohydrine reacted more easily with sodium ethoxide catalyst. After previous conversion of alcohols to the sodium salts, the reaction with epichlorohydrine was also unsuccessful. On the other hand, Kuwamura[7] has reported that higher alcohols reacted with epichlorohydrine in the presence of stannic chloride catalyst to give α-alkyl-α′-chlorohydrine (VI), followed by the conversion to the corresponding epoxides by treating with sodium hydroxide. According to this procedure, lower alcohols were also readily converted to 2,3-epoxypropyl alkyl ether (VII—IX) by treating with epichlorohydrine in 60—70% yields. These epoxides exhibited the infrared (IR) absorptions characteristic to the epoxide ring at 1250 cm^{-1}, 890 cm^{-1} and 830 cm^{-1} and assignable to the ether group at 1050 cm^{-1}. The nuclear magnetic resonance (NMR) spectra also exhibited the typical 1-substituted ethylene oxide ring pattern (ABX system), the qualtet (J=4 cps, J=8 cps) of two pairs at τ 7.30—6.80 and the multiplet (J=4 cps) of two pairs of peaks of roughly equal size at τ 6.70—6.30.

These 2,3-epoxypropyl alkyl ether, 2,3-epoxypropyl aryl ether and 2,3-epoxypropyl alkyl thioether obtained were attempted to react with several Schiff bases, such as benzalaniline, benzal-*p*-anisidine, benzal-*p*-phenetidine and benzal-*p*-chloroaniline, according to the reverse procedure of Oda method,[4] because some epoxides were difficult to dissolve in carbon tetrachloride as a solvent. Thus, by adding Lewis acid to a stirred suspension of 2,3-epoxypropyl aryl ether and Schiff base in carbon tetrachloride at 10°, the corresponding oxazolidines were obtained in 40—75% yields, though 2,3-epoxypropyl alkyl ether and 2,3-epoxypropyl alkyl thioether were unsuccessful to react with Schiff base to recover the unreacted materials.

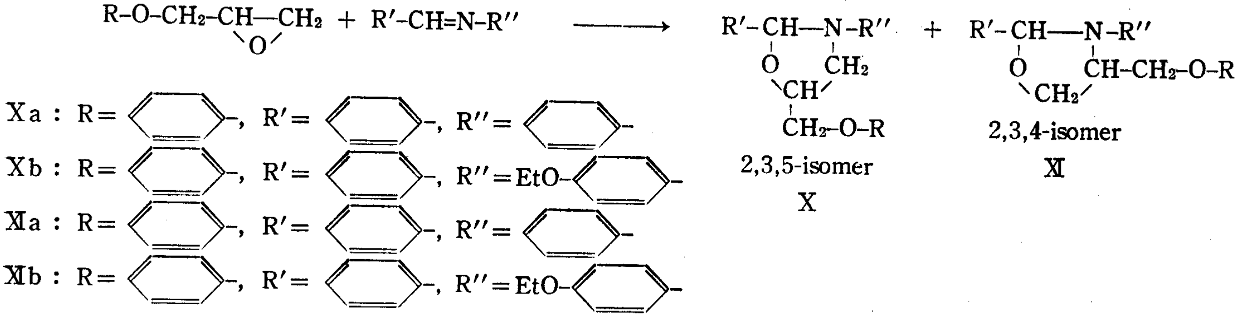

Chart 2

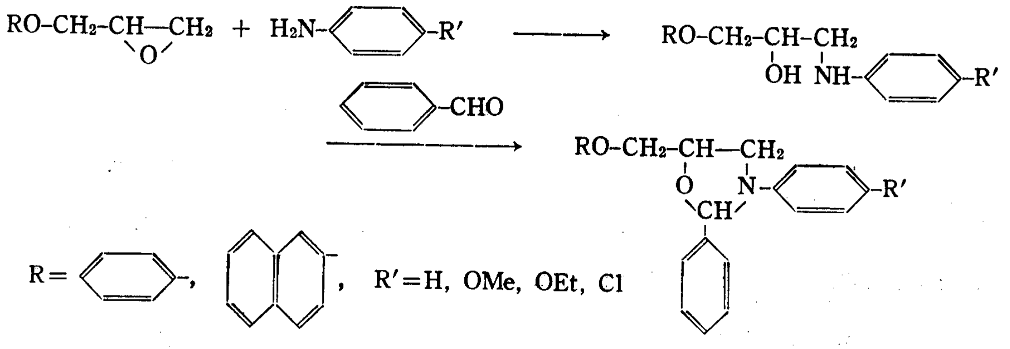

Chart 3

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5) Y. Iwakura and S. Izawa, *J. Org. Chem.*, **29**, 379 (1964).
6) Y. Iwakura, S. Izawa and F. Hayano, *J. Poly. Scie.*, **4**, 751 (1966).
7) T. Kuwamura, *J. Chem. Soc. Japan*, **63**, 595 (1960).

In the reaction of epoxide with Schiff base, two isomers of the product, *i.e.*, 2,3,5-trisubstituted and 2,3,4-trisubstituted oxazolidines, are possible. In fact, the reaction of 2,3-epoxypropyl phenyl ether (I) with benzal-*p*-phenetidine afforded two isomeric oxazolidines (Xb, XIb) melting at 90—92° and 91—93° in 40% and 21% yields, respectively (Chart 2). The calculated value of the analyses of the two isomers is completely same and the experimental value of the compounds obtained agreed with the calculated value. Both of the IR and NMR spectra of two compounds obtained also exhibited almost same patterns as shown in Fig. 1. Therefore, it is evident that these compounds are 2-phenyl-3-*p*-ethoxyphenyl-5-phenoxymethyloxazolidine and 2-phenyl-3-*p*-ethoxyphenyl-4-phenoxymethyloxazolidine (Xb and XIb). A similar orientation was observed on the addition of the same epoxide to benzalaniline, giving 2,3-diphenyl-5-phenoxymethyloxazolidine (Xa) and 2,3-diphenyl-4-phenoxymethyloxazolidine (XIa) in 61% and 6% yields, respectively. For the assignment of the structure, the authentic compounds of 2-phenyl-3-*p*-ethoxyphenyl-5-phenoxymethyloxazolidine (Xb)[8–10] and 2,3-diphenyl-5-phenoxymethyloxazolidine (Xa)[8–10] were prepared by another reaction as follow. By mixed melting point determination with these compounds, the structure of the isomers was decided. The predominant ring-opening at primary carbon suggests that the orientation is much influenced by the electron-withdrawing phenoxy group.

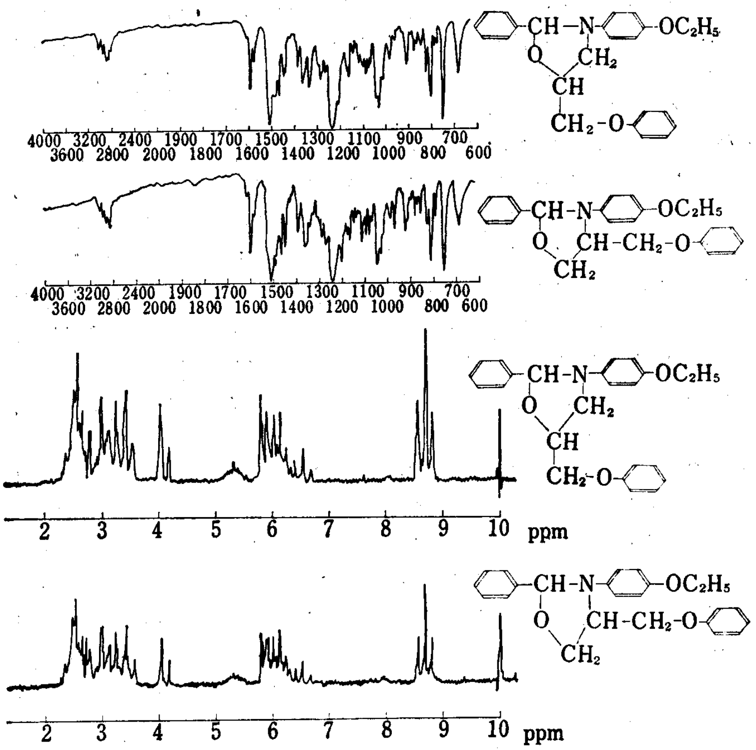

Fig. 1. IR and NMR Spectra of 2-Phenyl-3-*p*-ethoxyphenyl-5-phenoxymethyloxazolidine and 2-Phenyl-3-*p*-ethoxyphenyl-4-phenoxymethyloxazolidine

The whole oxazolidines obtained by the reaction of 2,3-epoxypropyl aryl ether with Schiff base were summarized in Table I.

Experimental

2,3-Epoxypropyl Phenyl Thioether (III)——To a mixture of 220 g (2.0 mole) of thiophenol and 500 g (5.34 mole) of epichlorohydrine was added dropwise with stirring 108 g (2.0 mole) of sodium methoxide in 800 ml of MeOH during 1 hr below 20°, and the mixture was stirred for an additional 1 hr. After removal of an excess of epichlorohydrine, the residue was distilled under reduced pressure to give 126 g (76%) of a colorless liquid boiling at 106—107°/5 mm. IR ν_{max}^{film} cm^{-1}: 1250, 920, 840 $(\underset{\diagdown O \diagup}{\mathrm{C—C}})$. *Anal.* Calcd. for $C_9H_{10}OS$: C, 65.05; H, 6.07. Found: C, 64.59; H, 5.78.

2,3-Epoxypropyl Benzyl Thioether (IV)——A mixture of 250 g (2.0 mole) of benzylthiol and 500 g (5.34 mole) of epichlorohydrine was treated with 108 g (2.0 mole) of sodium methoxide by the same procedure as described above to give 124 g (69%) of a colorless liquid boiling at 111°/5 mm. IR ν_{max}^{film} cm^{-1}: 1250,

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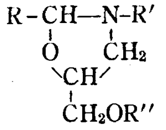
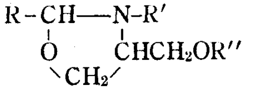
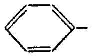
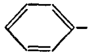
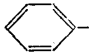
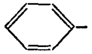
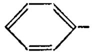
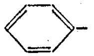
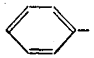
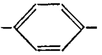
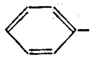
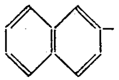
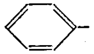
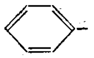
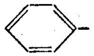
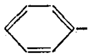
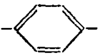
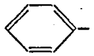
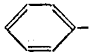
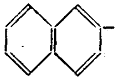
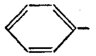
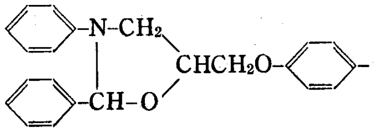
8) E. Bergmann, E. Zimkin and S. Pinchas, *Rec. Trav. Chim.*, **71**, 168 (1952).
9) A.C. Cope and E.M. Hancock, *J. Am. Chem. Soc.*, **64**, 1503 (1902).
10) E.M. Hancock and A.C. Cope, *J. Am. Chem. Soc.*, **66**, 1738 (1944).

TABLE I

 (A)

 (B)

R	R′	R″	Yield (%)	mp (°C)	Type	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
			6.0	76—79	A	$C_{22}H_{21}O_2N$	79.47	6.37	4.22	79.61	6.36	4.60
			55.3	105.5—107.5	B	$C_{22}H_{21}O_2N$	79.47	6.37	4.22	79.48	6.20	4.32
		CH_3-	58.5	93.5—94.5	A	$C_{23}H_{23}O_2N$	79.96	6.71	4.06	79.79	6.75	4.27
			74.6	105—105.5	A	$C_{26}H_{23}O_2N$	81.85	6.06	3.68	82.11	6.17	3.76
	CH_3O-		42.3	100—102	A	$C_{23}H_{23}O_3N$	75.62	6.63	4.01	75.71	6.23	4.02
	C_2H_5O-		40.1	91—93	A	$C_{24}H_{25}O_3N$	76.99	6.68	3.74	77.39	6.55	3.92
	C_2H_5O-		21.0	90—92	B	$C_{24}H_{25}O_3N$	76.99	6.68	3.74	77.09	6.55	4.20
	Cl-		63.5	101—103	A	$C_{22}H_{20}O_2NCl$	72.60	5.70	3.96	72.31	5.37	3.99
	CH_3O-		43.2	107.5—109.5	A	$C_{27}H_{25}O_3N$	78.81	6.13	3.41	78.89	5.98	3.56
			42.8	180.5—182.5	A	$C_{32}H_{34}O_4N_2$	77.11	6.74	4.99	77.00	6.38	5.27

920, 840 $(\underset{\diagdown O \diagup}{C—C})$. *Anal.* Calcd. for $C_{10}H_{12}OS$: C, 66.65; H, 6.71. Found: C, 66.52; H, 6.82.

2,3-Epoxypropyl *t*-Butyl Thioether (V)——A mixture of 90 g (1.0 mole) of *t*-butylthiol and 200 g (2.14 mole) of epichlorohydrine was treated with 54 g (1.0 mole) of sodium methoxide by the same procedure as described above to obtain 85 g (58%) of a colorless liquid boiling at 56—58°/3 mm. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1265, 950, 835 $(\underset{\diagdown O \diagup}{C—C})$. *Anal.* Calcd. for $C_7H_{14}OS$: C, 57.51; H, 9.65. Found: C, 57.23; H, 9.84.

2,3-Epoxypropyl *t*-Butyl Ether (VII)——To a mixture of 222 g (3.0 mole) of *t*-butanol and 2.6 g (0.01 mole) of $SnCl_4$ was added dropwise with stirring 93.5 g (1.0 mole) of epichlorohydrine during 5—10 min. at 10—20°, and the mixture was heated for 1 hr under reflux. After cooling, the mixture was stirred with a small amount of H_2O, dried over Na_2SO_4 and evaporated to remove an excess of *t*-butanol under reduced pressure. The residue was distilled under reduced pressure to give 250 g (75%) of 1-*t*-butoxy-3-chloro-2-propanol boiling at 105—109°/40 min. To 250 g (1.5 mole) of 1-*t*-butoxy-3-chloro-2-propanol was added dropwise with stirring 25% aqueous solution of 60 g (1.5 mole) of NaOH during 20—30 min. at 85—90°, and the mixture was vigorously stirred for an additional 1.5 hr at 95—100°. On cooling the mixture was separated into two layers. The upper layer was isolated, dried over anhyd. Na_2CO_3 and distilled under reduced pressure to give 166 g (85%) of a colorless liquid boiling at 57°/20 mm. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1250, 910, 845 $(\underset{\diagdown O \diagup}{C—C})$. *Anal.* Calcd. for $C_7H_{14}O_2$: C, 64.58; H, 10.84. Found: C, 64.35; H, 10.62.

2,3-Epoxypropyl Benzyl Ether (IX)——By the procedure described above, a mixture of 486 g (4.5 mole) of benzylalcohol and 140 g (1.5 mole) of epichlorohydrine was treated with 2.9 g (0.015 mole) of $SnCl_4$ to give 210 g (70%) of 1-benzyloxy-3-chloro-2-propanol boiling at 120—127°/3 mm, which was then converted with 25% NaOH solution to 2,3-epoxypropyl benzyl ether boiling at 108°/5 mm in 80% (138 g) yield. IR $\nu_{\max}^{\text{film}}$ cm^{-1}: 1240, 890, 830 $(\underset{\diagdown O \diagup}{C—C})$. *Anal.* Calcd. for $C_{10}H_{12}O_2$: C, 73.14; H, 7.37. Found: C, 73.09; H, 7.28.

2,3-Diphenyl-5-phenoxymethyloxazolidine and 2,3-Diphenyl-4-phenoxymethyloxazolidine——To a solution of 16.5 g (0.11 mole) of 2,3-epoxypropyl phenyl ether and 18.1 g (0.1 mole) of benzalaniline in 40 ml of CCl_4 was added dropwise with stirring a solution of 1.3 g (0.005 mole) of $SnCl_4$ in 20 ml of CCl_4 during 1.5 hr below 10°, and the mixture was stirred for an additional 2 hr at 20°. The mixture was poured into 100 ml of H_2O and basified with stirring with dil. KOH. The CCl_4 layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. To the residue was added 200 ml of EtOH to give 18.3 g (55.3%) of 2,3-diphenyl-5-phenoxymethyloxazolidine melting at 76—79° and 2.0 g (6%) of 2,3-diphenyl-4-phenoxymethyloxazolidine melting at 105.5—107.5°. 2,3-Diphenyl-5-phenoxymethyloxazolidine: IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1179, 1126, 1099 (O-C-N). *Anal.* Calcd. for $C_{22}H_{21}O_2N$: C, 79.47; H, 6.37; N, 4.22. Found: C, 79.48; H, 6.20; N, 4.32. 2,3-Diphenyl-4-phenoxymethyloxazolidine; IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1173, 1122, 1100 (O-C-N). *Anal.* Calcd. for $C_{22}H_{21}O_2N$: C, 79.47; H, 6.37; N, 4.22. Found: C, 79.61; H, 6.36; N, 4.60.

2,3-Diphenyl-5-*p*-tolyloxymethyloxazolidine——A mixture of 16.5 g (0.11 mole) of 2,3-epoxypropyl phenyl ether and 19.5 g (0.1 mole) of benzal-*p*-toluidine was treated with 1.3 g (0.005 mole) of $SnCl_4$ by the same procedure as described above. Recrystallization from CCl_4–EtOH gave 20.2 g (58.5%) of colorless needles melting at 93.5—94.5°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1176, 1123, 1095 (O-C-N). *Anal.* Calcd. for $C_{23}H_{23}O_2N$: C, 79.96; H, 6.71; N, 4.06. Found: C, 79.79; H, 6.75; N, 4.27.

2,3-Diphenyl-5-*β*-naphthoxymethyloxazolidine——To a solution of 11 g (0.055 mole) of 2,3-epoxypropyl *β*-naphthyl ether and 9.1 g (0.05 mole) of benzalaniline in 60 ml of CCl_4 was added dropwise with stirring a solution of 0.7 g (0.0025 mole) of $SnCl_4$ during 15 min. at 8—10°, and the mixture was stirred for 2 hr at 20°. The mixture was then poured into 1 liter of H_2O. The CCl_4 layer separated was washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. To the residue was added 500 ml of cold EtOH, and the precipitates deposited were recrystallized from CCl_4–EtOH to give 14.6 g (74.6%) of colorless needles melting at 105—105.5°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1183, 1123, 1104 (O-C-N). *Anal.* Calcd. for $C_{26}H_{23}O_2N$: C, 81.85; H, 6.06; N, 3.68. Found: C, 82.11; H, 6.17; N, 3.76.

2-Phenyl-3-*p*-methoxyphenyl-5-phenoxymethyloxazolidine——To a solution of 3.0 g (0.02 mole) of 2,3-epoxypropyl phenyl ether and 4.2 g (0.022 mole) of benzal-*p*-anisidine in 50 ml of CCl_4 was added dropwise with stirring a solution of 0.3 g (0.001 mole) of $SnCl_4$ in 10 ml of CCl_4 during 5 min. below 10°, and the mixture was stirred for 3 hr at 20°. The mixture was poured into 50 ml of H_2O and basified with dil. KOH. The CCl_4 layer was separated, washed with H_2O, dried over Na_2SO_4 and evaporated to dryness. The residue was recrystallized from CCl_4–EtOH to give 3.0 g (42%) of colorless needles melting at 100—102°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1175, 1125, 1097 (O-CON). *Anal.* Calcd. for $C_{23}H_{23}O_3N$: C, 75.62; H, 6.63; N, 4.01. Found: C, 75.71; H, 6.23; N, 4.02.

2-Phenyl-3-*p*-ethoxyphenyl-5-phenoxymethyloxazolidine and 2-Phenyl-3-*p*-ethoxyphenyl-4-phenoxymethyloxazolidine——A mixture of 3.0 g (0.02 mole) of 2,3-epoxypropyl phenyl ether and 4.5 g (0.022 mole) of benzal-*p*-phenethidine was treated with 0.2 g (0.001 mole) of $SnCl_4$ by the same procedure as described above. Recrystallization from EtOH gave 3.0 g (40%) of 2-phenyl-3-*p*-ethoxyphenyl-5-phenoxymethyloxazolidine melting at 91—93°. IR $\nu_{\max}^{\text{KBr}}$ cm^{-1}: 1172, 1096 (O-C-N). *Anal.* Calcd. for $C_{24}H_{25}O_3N$: C, 76.99;

H, 6.68; N, 3.74. Found: C, 77.39; H, 6.55; N, 3.92. The insoluble solid in EtOH was recrystallized from CCl_4–EtOH to give 1.57 g (21%) of 2-phenyl-3-*p*-ethoxyphenyl-4-phenoxymethyloxazolidine melting at 90—92°. IR ν_{max}^{KBr} cm^{-1}: 1172, 1116, 1100 (O-C-N). *Anal.* Calcd. for $C_{24}H_{15}O_3N$: C, 76.99; H, 6.68; N, 3.74. Found: C, 77.09; H, 6.55; N, 4.02.

2-Phenyl-3-*p*-chlorophenyl-5-phenoxymethyloxazolidine——A mixture of 3.0 g (0.02 mole) of 2,3-epoxypropyl phenyl ether and 4.3 g (0.022 mole) of benzal-*p*-chloroaniline was treated with 0.3 g (0.001 mole) of $SnCl_4$ by the same procedure as described above. Recrystallization from EtOH gave 4.64 g (63.5%) of colorless needles melting at 101—103°. IR ν_{max}^{KBr} cm^{-1}: 1170, 1125, 1095 (O-C-N). *Anal.* Calcd. for $C_{22}H_{20}O_2NCl$: C, 72.60; H, 5.70; N, 3.96. Found: C, 72.31; H, 5.37; N, 3.99.

2-Phenyl-3-*p*-methoxyphenyl-5-*β*-naphthyloxymethyloxazolidine——A mixture of 4.4 g (0.02 mole) of 2,3-epoxypropyl *β*-naphthyl ether and 4.2 g (0.022 mole) of benzal-*p*-anisidine was also analogously treated with 0.3 g (0.001 mole) of $SnCl_4$. Recrystallization from EtOH gave 3.55 g (43.2%) of colorless needles melting at 107.5—109.5°. IR ν_{max}^{KBr} cm^{-1}: 1217, 1180, 1115 (O-C-N). *Anal.* Calcd. for $C_{27}H_{25}O_3N$: C, 78.81; H, 6.13; N, 3.41. Found: C, 78.89; H, 5.98; N, 3.56.

Another General Synthetic Procedure of 2-Phenyl-3-aryl-5-phenoxymethyloxazolidine——A solution of 0.03 mole of 2,3-epoxypropyl phenyl ether and 0.03 mole of arylamine in MeOH was heated for 3 hr under reflux. After removal of MeOH, 100 ml of benzene and then 0.03 mole of benzaldehyde was added to the residue and the mixture was heated under reflux until 0.03 mole of H_2O was collected in a water separator funnel. The mixture was evaporated to dryness and the residue was recrystallized from EtOH.

Acknowledgement The authors are indebted to Mrs. K. Shiraki and Yoshitomi Seiyaku Co., Ltd. for the microanalytical data and to Miss M. Sato for the measurements of IR spectra.

[Chem. Pharm. Bull. 19(11)2409—2411(1971)]

UDC 547.92.02.05 : 547.918.02.05

Steroidal Sapogenins of *Aletris spicata* (THUNB.) FRANCHET[1)]

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(Received March 6, 1971)

The genera Aletris and Metanarthecium both belong to the family Liliaceae. Although Franchet[3)] united Metanarthecium to Aletris, these two genera have commonly been considered as distinct by later botanists, some of whom[4)] have ever treated the two genera as the members of widely separated subfamilies, though Hutchinson[5)] classified them in the same tribe. One of main characters which has been used by botanists as a discriminating feature between the two genera is the degree of adhesion of the ovary to the perianth. Recently, Hara[6)] examined some of the Asian Aletris species and observed a wide variance in the length of the part of the perianth connate with the ovary. This led him to propose the reunion of Metanarthecium with Aletris.

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