New Addition Reactions. II. Addition of Aliphatic Epoxides to Schiff Bases

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Some studies of the formation of five-membered heterocycles by the addition of epoxides to aldehydes, ketones, esters and isocyanates have already been reported. We described in a previous paper¹⁾ the results of a new reaction of epoxides with ketene. By analogy, the addition of epoxides to Schiff bases may be expected to produce oxazolidines. In 1950, Doughty et al.²⁾ observed the formation of these compounds by a similar addition of ethylenimine to aldehydes or ketones. It has now been found that in the presence of catalytic amounts (5∼10 mol.%) of stannic chloride, the expected cyclization of aliphatic epoxides with Schiff bases proceeds smoothly, according to the following equation:

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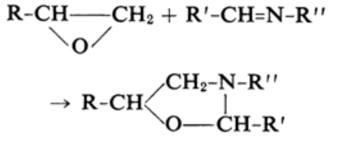
1) R. Oda, S. Munemiya and M. Okano, *J. Org. Chem.*, **26**, 1341 (1961).

2) J. B. Doughty, C. L. Lazzell and A. H. Collett, *J. Am. Chem. Soc.*, **72**, 2866 (1950).



All reactions were carried out in carbon tetrachloride at 10∼20°C for three hours. The results of several experiments are shown in Table I. Unfortunately, in a similar reaction with styrene oxide, the attempt to isolate the desired adduct was unsuccessful, probably because of contamination with a hydroxyl compound (see Experimental).

The yields in this addition were generally not very high, and they were not improved by varying the reaction temperature or time. The use of boron trifluoride as a catalyst resulted in a lower yield of the desired product. It is of interest to note that *N-tert*-butylazomethine is capable of reaction with epoxides, even in the absence of a catalyst. This may be due to its high nucleophilicity. In the case of the reaction with benzalaniline, a considerable amount (ca. 70∼90%) of the unreacted Schiff base could be recovered, but complete recovery was impossible because of the thermal instability of the product. On the other hand, when *N-tert*-butylazomethine was used as a Schiff base, a great loss (ca. 50%) of this compound was observed in a blank experiment, presumably due to simultaneous evaporation on distillation of the solvent and hydrolysis during the after-treatment. Therefore, no effort was made to recover it from the reaction mixture.

To ascertain the direction of the ring-opening of the substituted ethylene oxides, the adduct from propylene oxide and *N-tert*-butylazomethine was compared with two authentic specimens, i. e., 3-*tert*-butyl-4-methyl- and 3-*tert*-butyl-5-methyloxazolidines, prepared by the usual condensation method[3]. The results of mixed melting point determinations as their picrates showed that the product was the 3, 5-isomer. Moreover, vapor phase chromatographic analysis indicated that the liquid adduct did not contain any 3, 4-isomer. The structure of the solid propyleneoxide-benzalaniline adduct was also confirmed by independent synthesis from 1-anilino-2-propanol and benzaldehyde. In the case of epichlorohydrin, it has been shown that ring-opening always occurs at the primary position[4]; hence, the exclusive formation of the 3, 5-isomer would be expected.

Based on the observed orientation, an S_N2-like mechanism[5], which involves a nucleophilic attack by the Schiff base on the epoxide, may be postulated, but some additional evidence would seem to be desirable before a detailed mechanism can be proposed.

Experimental[6]

Some illustrative examples are given below.

3-*tert*-Butyl-5-methyloxazolidine.—A solution of 6.6 g. (0.025 mol.) of stannic chloride in 60 ml. of carbon tetrachloride was dropped over a period of 1 hr. into a stirred solution of 21.2 g. (0.25 mol.) of *N-tert*-butylazomethine (prepared by the procedure of Hurwitz[7]) and 15.9 g. (0.275 mol.) of propylene oxide in 100 ml. of carbon tetrachloride. The addition was carried out at 10∼15°C. After additional stirring for 2 hr. at 20°C, the solution was poured into 100 ml. of water, and filtered to remove stannic hydroxide. The aqueous layer was separated from the organic layer and extracted with 50 ml. of carbon tetrachloride. The combined carbon tetrachloride layers were washed with water, dried, and evaporated. Distillation in vacuo gave 8.6 g. (24%) of the base, b. p. 56∼57°C (20 mmHg). The picrate (monohydrate), after recrystallization from 98% ethanol, melted at 180°C. No mixed melting point depression was observed with the picrate of authentic 3-*tert*-butyl-5-methyloxazolidine, but there was a lower mixed melting point with the picrate of authentic 3-*tert*-butyl-4-methyloxazolidine.

Vapor phase chromatographic analysis of the crude distillate was carried out, using a 1-meter column containing polyethylene glycol 1500-Celite 545 (3 : 7 by weight), with nitrogen as a carrier gas, at 70°C. The chromatogram indicated that the product consisted mainly of the 3, 5-isomer. No trace of the 3, 4-isomer was detected.

In this case, the authentic 3, 5-isomer was synthesized by condensation between 1-bromo-2-propanol and *tert*-butylamine, followed by cyclization with formaldehyde. The pure base boiled at 53∼54°C (15 mmHg), and its picrate (monohydrate) melted at 180∼181°C (Analytical data are included in Table I). The authentic 3, 4-isomer was similarly prepared from ethyl α-bromopropionate, via ethyl α-(*N-tert*-butyl)aminopropionate and 2-(*N-tert*-butyl)aminopropanol. The pure base boiled at 52∼53°C (19 mmHg), and its picrate melted at 185∼186°C.

The free base. Found: C, 67.01; H, 12.18; N, 9.56. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78%. The picrate. Found: C, 45.20; H, 5.57; N, 15.03. Calcd. for $C_{14}H_{20}N_4O_8$: C, 45.16; H, 5.41; N, 15.05%.

5-Methyl-2, 3-diphenyloxazolidine. — A solution of 3.3 g. (0.0125 mol.) of stannic chloride in 30 ml. of carbon tetrachloride was added, drop by drop, over a period of 1 hr., to a solution of 45.3 g. (0.25 mol.) of benzalaniline and 15.9 g. (0.275 mol.) of propylene oxide in 100 ml. of carbon tetrachloride maintained at 10°C. Stirring was continued at

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[3] Cf. R. C. Elderfield, "Heterocyclic Compounds", Vol. 5, John Wiley, New York, N. Y. (1957), p. 391.

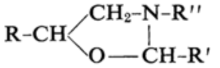
[4] "Epichlorohydrin", Shell Chem. Corp., New York, N. Y. (1949).

[5] Cf. R. E. Parker and N. S. Isaacs, *Chem. Revs.*, **59**, 742 (1959).

[6] All temperatures are uncorrected.

[7] M. D. Hurwitz, U. S. Pat., 2582128 (1952); *Chem. Abstr.*, **46**, 8146 (1952).

TABLE I. FORMATION OF OXAZOLIDINES FROM ALIPHATIC EPOXIDES AND SCHIFF BASES



R in epoxide[a]	R′ and R″ in Schiff base	Catalyst (Mol.%)[b]	Yield[c] %	B. p., °C (mmHg)	M. p. of picrate, °C
R=H[d]	R′=H, R″=$(CH_3)_3C$	$SnCl_4$ (10)	18	63～64(32)[e]	155[f]
R=H[d]	R′=H, R″=$(CH_3)_3C$	None	6	60～61(27)	155
R=CH_3	R′=H, R″=$(CH_3)_3C$	$SnCl_4$ (10)	24	56～57(20)[g]	180[h]
R=CH_3	R′=H, R″=$(CH_3)_3C$	BF_3 (100)	8	56～57(20)	180
R=CH_3	R′=H, R″=$(CH_3)_3C$	None	4	51～52(15)	180
R=CH_2Cl	R′=H, R″=$(CH_3)_3C$	$SnCl_4$ (10)	59	93～94(19)[i]	156[j]
R=H[d]	R′=R″=C_6H_5	$SnCl_4$ (5)	14(37)	84[k,l]	
R=CH_3	R′=R″=C_6H_5	$SnCl_4$ (5)	30(79)	88[k,m]	
R=CH_3	R′=R″=C_6H_5	None	Unreacted		
R=CH_2Cl	R′=R″=C_6H_5	$SnCl_4$ (5)	70	114～115[k,n]	
R=CH_2Cl	R′=R″=C_6H_5	BF_3 (10)	25(63)	114～115[k]	

a Ten mol.% excess of epoxides were used, unless otherwise indicated.
b Based on Schiff bases.
c Conversions based on consumed benzalaniline are shown in parentheses.
d Two equivalents of epoxide were used, because of its low boiling point.
e Found: C, 65.03; H, 11.73; N, 10.92. Calcd. for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84%.
f Monohydrate. Found: C, 41.73; H, 5.33; N, 15.01. Calcd. for $C_{13}H_{20}N_4O_9$: C, 41.49; H, 5.36; N, 14.89%.
g Found: C, 66.84; H, 11.70; N, 9.93. Calcd. for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78%.
h Monohydrate. Found: C, 43.17; H, 5.77; N, 14.62. Calcd. for $C_{14}H_{22}N_4O_9$: C, 43.07; H, 5.68; N, 14.35%.
i Found: C, 53.79; H, 9.30; N, 7.66; Cl, 20.05. Calcd. for $C_8H_{16}NOCl$: C, 54.07; H, 9.08; N, 7.88; Cl, 19.91%.
j Monohydrate. Found: C, 39.79; H, 5.11; N, 13.89; Cl, 8.70. Calcd. for $C_{14}H_{21}N_4O_9Cl$: C, 39.59; H, 4.99; N, 13.16; Cl, 8.35%.
k M. p.
l Reported m. p. 84～85°C [G. A. R. Kon and J. J. Roberts, *J. Chem. Soc.*, **1950**, 980].
m Reported m. p. 88.5～89.5°C (Ref. 8).
n Found: C, 70.00; H, 6.04; N, 5.22; Cl, 13.23. Calcd. for $C_{16}H_{16}NOCl$: C, 70.19; H, 5.89; N, 5.12; Cl, 12.95%.

20°C for an additional 2 hr. The reaction mixture was then poured into 100 ml. of water, made slightly basic with aqueous potassium hydroxide, and filtered. The organic layer was washed, dried, evaporated and distilled in vacuo to remove unreacted benzalaniline (28 g.). Recrystallization of the residue from ethanol afforded 18.0 g. (30%) of the product, m. p. 88°C. A mixed melting point with the authentic material prepared by condensation between 1-anilino-2-propanol and benzaldehyde[8] showed no depression.

5-Chloromethyl-2,3-diphenyloxazolidine.—The procedure employed was similar to that used for the preparation of 5-methyl-2,3-diphenyloxazolidine, except that 25.4 g. (0.275 mol.) of epichlorohydrin was employed. The product which separated from the carbon tetrachloride solution at the end of reaction was filtered, washed with water, and dried. Some additional product was also obtained from the solvent layer. Recrystallization from an ethanol-dimethylformamide mixture gave 47.8 g. (70%) of pale yellow crystals, m. p. 114～115°C.

An Attempt to Prepare the Adduct from Styrene Oxide and *N-tert*-Butylazomethine.—In a similar way, 33 g. of styrene oxide was treated with 21.2 g. of *N-tert*-butylazomethine in the presence of a stannic chloride catalyst. The isolated basic fraction, b. p. 111～113°C (4 mmHg), weighed 8.5 g. Even after duplicate vacuum distillations, its elemental analysis disagreed with that of the expected adduct. However, the infrared spectrum was similar to those of other 3-*tert*-butyloxazolidines except for the appearance of a strong hydroxyl absorption in the 3400 cm^{-1} region. The picrate obtained from this product melted at 152～154°C and showed analytical data corresponding to the picrate of the desired adduct.

Found: C, 52.69; H, 5.35; N, 12.61. Calcd. for $C_{19}H_{22}N_4O_8$: C, 52.53; H, 5.10; N, 12.90%.

No further study of the structure of the product was undertaken.

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[8] K. D. Petrov, *Sbornik Stateĭ Obshcheĭ Khim., Akad. Nauk. S. S. S. R.*, **1**, 374 (1953); *Chem. Abstr.*, **49**, 997 (1955).