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2-Oxazolidones from Glycidyl Ether Reactions with Acid Amides

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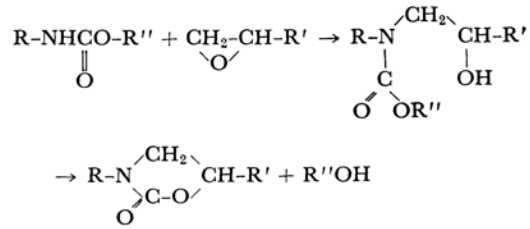
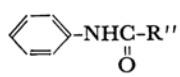
The reaction between acid amides and aryl glycidyl ethers was carried out using tertiary amine as the catalyst. 2-Oxazolidone derivatives were obtained by the reaction of trichloroacetanilide or trifluoroacetanilide with aryl glycidyl ether. Acyl migration occurred in the reaction of acetanilide with phenyl glycidyl ether.

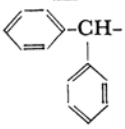
In a previous paper[1] we reported that 2-oxazolidone ring formation occurred in the reaction between epoxides and urethans. The reaction has been shown to proceed through a nucleophilic attack of the imide group of urethans on an epoxy ring, followed by an intramolecular exchange of alcohols with a carbon-oxygen bond scission in urethan linkage. Keeping in mind that the epoxides can react with the imide groups of urethans under the catalysis of tertiary amines, and that acid amides and urethans have the same imide groups, the reactivity of the epoxy ring with acid amide will be studied here.



A mixture of equimolar acetanilide and phenyl glycidyl ether, with a small amount of triethylamine as a catalyst, was heated at 100°C for 5 hr. The infrared spectra of the reaction mixture showed an

TABLE I



R''	M. p.,	(Lit.)	Anal. of N, % Calcd.	Found	Results of the reaction with phenyl glycidyl ether at 100°C for 2 hr.
CH_3-	113—114	(114)	10.37	10.31	Gave V, VII[a]
	131—132	(134)	8.26	8.41	Gave V, VII
Cl- 	116—117	(117)	6.86	7.01	Gave V, VII
	91—93	(94)	5.87	5.98	Gave V, VII and a little amounut of IV
$ClCH_2$-	163.5—164	(164)	7.11	7.07	Side reaction[b]
Cl_2CH-	208—209	(204)	11.57	11.39	Side reaction[c]
Cl_3C-	193—194	(194)	6.05	6.29	Gave IV in good yield[d]
O_2N- 	179—180	(180)	4.88	4.78	Side reaction[c]
O_2N-  -CH_2-	205—206		10.93	10.68	Side reaction[c]
F_3C-	88—89	(91)	7.41	7.27	Gave IV in good yield[d]
HCF_2CF_2-	66—68	(69)	6.33	6.45	Side reaction[c]
NC-CH_2-	194—195	(198)	17.49	17.53	Side reaction[c]

a) Identified by preparing acetates (VIa and VIIIa).
b) *N,N'*-diphenyldiketopiperazine was obtained in good yield.
c) It was difficult to estimate the structure of products from the infrared spectra of reaction mixture.
d) 3-Phenyl-5-phenoxymethyl-2-oxazolidone was obtained quantitatively.

1) Y. Iwakura and S. Izawa, *J. Org. Chem.*, **29**, 379 (1964).

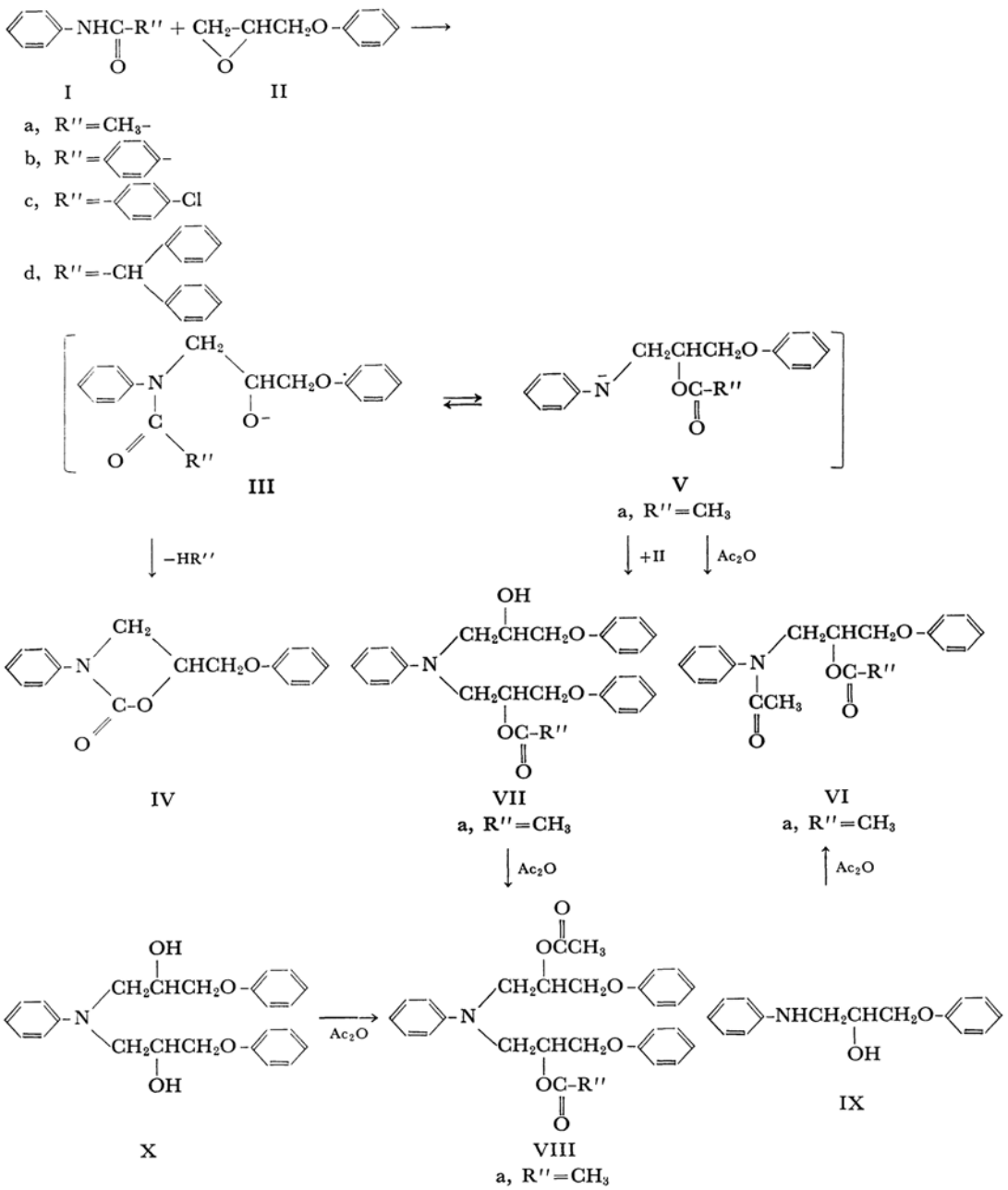


Chart 1

appearance of a new strong absorption at 1735 cm^{-1} and a decrease in the intensity of the amide band of the starting material. The acetylation of the products without separation gave VIa and VIIIa, as Chart 1 shows. The structure of VIa and VIIIa were confirmed to be diacetates of *N*-(3-phenoxy-2-hydroxypropyl)aniline (IX) and *N*, *N*-bis(3-phenoxy-2-hydroxypropyl)aniline (X) respectively, by comparing the melting point and the infrared spectra with the authentic samples prepared via the acetylation of IX and X according to Kier and Penland's method.[2]

These results suggested that the nucleophilic attack of the imide group of acid amide on the epoxy ring occurred easily as had been expected, but that the intramolecular acyl migration reaction proceeded exclusively in the intermediate, III, to give esteramine (Va), since carbon-carbon bond scission was difficult. Further reaction of

2) L. B. Kier and R. B. Penland, ibid., **25**, 1865 (1960).

TABLE II

R-NHC-R''
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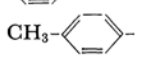
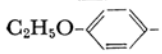
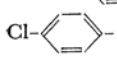
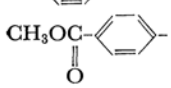
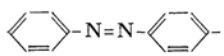
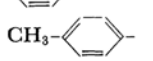
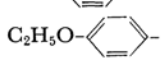
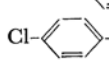
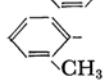
R	R''	M.p., °C	Formula	Anal., % Calcd. / Found C	H	N	Products of the reaction with phenyl glycidyl ether at 130°C for 2 hr.
	Cl_3C-	91—93	$C_8H_6Cl_3NO$	40.28 40.58	2.54 2.58	5.87 5.98	2-Oxazolidone[a]
	Cl_3C-	110.5—111.5	$C_9H_8Cl_3NO$	42.80 42.89	3.19 3.22	5.55 5.66	2-Oxazolidone
	Cl_3C-	124—126	$C_{10}H_{10}Cl_3NO_2$	42.50 42.69	3.57 3.71	4.96 5.20	2-Oxazolidone
	Cl_3C-	124.5—125.5	$C_8H_5Cl_4NO$	35.20 35.33	1.85 1.81	5.13 5.25	2-Oxazolidone
	Cl_3C-	115—118	$C_{10}H_8Cl_3NO_3$	40.50 40.46	2.72 2.84	4.72 4.58	2-Oxazolidone[b]
	Cl_3C-	143—145	$C_{14}H_{10}Cl_3N_3O$	49.08 49.27	2.94 2.96	12.27 12.55	2-Oxazolidone[c]
	F_3C-	88—89	$C_8H_6F_3NO$	50.80 50.88	3.20 3.31	7.41 7.27	2-Oxazolidone
	F_3C-	109—111	$C_9H_8F_3NO$	53.20 53.37	3.97 3.94	6.89 7.08	2-Oxazolidone
	F_3C-	139—140	$C_{10}H_{10}F_3NO_2$	51.50 51.22	4.32 4.40	6.01 5.93	2-Oxazolidone
	F_3C-	122—123	$C_8H_5ClF_3NO$	42.97 43.05	2.25 2.35	6.27 6.59	2-Oxazolidone
	F_3C-	79—80	$C_9H_8F_3NO$	53.20 53.30	3.97 3.92	6.89 6.90	No reaction[d]

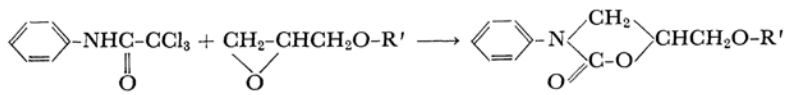
a) 2-Oxazolidones were identified by comparing melting point and infrared spectra with authentic samples.

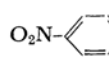
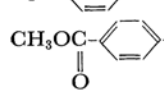
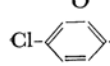
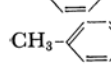
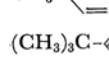
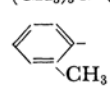
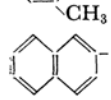
b) 3-(*p*-Methoxycarbonylphenyl)-5-phenoxymethyl-2-oxazolidone was recrystallized from ethanol, m. p. 195—197°C. Found: C, 65.94; H, 5.23; N, 4.17. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28%.

c) 3-(*p*-Phenylazophenyl)-5-phenoxymethyl-2-oxazolidone was recrystallized from ethanol, m. p. 184—186°C. Found: C, 70.69; H, 5.16; N, 11.32. Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H. 5.13; N, 11.25%.

d) The acid amide employed was recovered quantitatively.

TABLE III



R'	Reaction temp. °C	Reaction time hr.	Yield, %	M. p., °C	Formula	Anal., % Calcd. / Found C	H	N
	90	5	70	198—199	$C_{16}H_{14}N_2O_5$	61.14 61.16	4.49 4.61	8.91 8.97
	95	4	78	144—146	$C_{18}H_{17}NO_5$	66.05 65.83	5.24 5.31	4.28 4.34
	95	5	75	192—194	$C_{16}H_{14}ClNO_3$	63.25 63.46	4.64 4.83	4.61 4.63
	90	6	85	197—198	$C_{17}H_{17}NO_3$	72.06 72.26	6.05 6.28	4.94 4.96
	90	6	80	138—140	$C_{20}H_{23}NO_3$	73.82 73.52	7.12 7.10	4.30 4.24
	90	6	73	91—94	$C_{17}H_{17}NO_3$	72.06 72.35	6.05 6.10	4.94 5.11
	90	6	88	206—208	$C_{20}H_{17}NO_3$	75.25 75.37	5.37 5.37	4.39 4.47

Va with phenyl glycidyl ether occurred, yielding VIIa because the reactivity of the imino group of Va was higher than that of Ia.

In order to investigate the possibility of carbon-carbon bond scission in the reaction intermediate, III, an electron-withdrawing group was introduced into the acid component of acid amides. The acid amides prepared and the results of the reaction between these compounds and phenyl glycidyl ether are listed in Table I. The fact that only trifluoro- and trichloroacetanilides gave the 2-oxazolidone derivatives (IV) shows that a moderately strong electron-withdrawing ability is necessary to break the carbon-carbon bond in the intermediate, III.

The infrared spectra of the reaction mixture between phenyl glycidyl ether and *p*-nitrobenzanilide, *p*-nitrophenylacetanilide, dichloroacetanilide, 1, 1, 2, 2-tetrafluoropropionanilide, and cyanoacetanilide showed that some side reactions occurred, but they were not studied further.

N-Aryl-trichloroacetamides and *N*-aryl-trifluoroacetamides were prepared by the condensation of the corresponding amines and trichloro- or trifluoroacetyl chlorides. The reaction between these amides and phenyl glycidyl ether gave 3-aryl-5-phenoxymethyl-2-oxazolidones in good yields, as had been expected. The results are listed in Table II.

Trichloroacetanilide and aryl glycidyl ethers also produced 3-phenyl-5-aryloxymethyl-2-oxazolidones, as Table III shows.

Experimental

Glycidyl Ethers.—These were prepared by the condensation of the corresponding phenols and epichlorohydrin, as has been described in our previous paper.[1] A typical preparation will be described below.

***p*-Chlorophenyl Glycidyl Ether.**—To a mixture of 128.5 g. (1.0 mol.) of *p*-chlorophenol and 370 g. (4 mol.) of epichlorohydrin was added 54 g. (1.0 mol.) of sodium methylate in 400 ml. of methanol drop by drop with stirring during 1-hr. period at room temperature; the mixture was then stirred for an additional 1 hr. After the epichlorohydrin had been removed, the residue was distilled under reduced pressure to give 144 g. (78%) of *p*-chlorophenyl glycidyl ether, b. p. 115—116°C/2 mmHg; n_D^{25} 1.5419.

Acid Amides.—These were prepared by the condensation reaction of the corresponding amines with acid chlorides. Examples will be shown below.

***α*-Chloroacetanilide.**—To a solution of 22.6 g. (0.2 mol.) of monochloroacetyl chloride in 100 ml. of benzene was added 18.6 g. (0.2 mol.) of aniline and 20.2 g. (0.2 mol.) of triethylamine in 200 ml. of benzene with stirring at 10—20°C; the mixture was then allowed to stand for 3 hr. After the triethylamine hydrochloride had been filtered out and the benzene removed, the resulting crystalline solid was recrystallized from water to give 21.7 g. (64%) of *α*-chloroacetanilide, m. p. 163.5—164°C.

***α, α, α*-Trifluoroacetanilide.**—To a solution of 9.3 g. (0.1 mol.) of aniline and 10.1 g. (0.1 mol.) of triethylamine in 100 ml. of acetone was added 13.3 g. (0.1 mol.) of trifluoroacetyl chloride in 60 ml. of acetone with stirring at −10°C. The mixture was then allowed to stand for 1 hr. at room temperature. After the triethylamine hydrochloride had been filtered out and the acetone had been removed, the resulting crystalline solid was recrystallized from *n*-hexane to give 40.7 g. (72%) of *α, α, α*-trifluoro-*p*-ethoxyacetanilide, m. p. 139—140°C.

The Reaction between Acid Amides and Glycidyl Ethers.—A mixture of equimolar amounts of acid amide and glycidyl ether, with triethylenediamine as a catalyst, was heated at 100°C for 2 hr. An example will be shown below.

The Reaction of Phenyl Glycidyl Ether with Acetanilide.—A mixture of 13.5 g. (0.1 mol.) of acetanilide and 15.0 g. (0.1 mol.) of phenyl glycidyl ether was heated at 100°C in order to dissolve both ingredients, and then 0.1 g. of triethylenediamine was added. The mixture was heated at 100°C for 2 hr. After cooling, the reaction mixture was poured into a solution of 100 g. of acetic anhydride in 80 g. of pyridine and allowed to stand overnight at room temperature. Pyridine and acetic anhydride were removed by distillation under reduced pressure, and the residue was recrystallized from ethyl acetate to give 9.5 g. of *N, N*-bis(3-phenoxy-2-hydroxypropyl)aniline diacetate (VIIIa). After the ethyl acetate had been evaporated from the filtrate, the residue was recrystallized from ethanol to give 9.8 g. *N*-(3-phenoxy-2-hydroxypropyl)aniline diacetate (VIa). Acetanilide (4.1 g.) was recovered from the filtrate. The structures of VIa and VIIIa were confirmed by a mixed-melting-point determination and by comparing the infrared spectra with those of authentic samples.

The Preparation of Authentic Samples (VIa and VIIIa).—*N-(3-Phenoxy-2-hydroxypropyl)aniline Diacetate (VIa).*—To 9.5 g. (0.1 mol.) of redistilled aniline, which was maintained at 120°C, 4.5 g. (0.03 mol.) of phenyl glycidyl ether was added over 1-hr. period. The mixture was then heated for an additional 15 min. and distilled at 10 mmHg to recover the unreacted aniline. The pressure was then reduced further, and 6.5 g. of a viscous oil, b. p. 180—185°C (0.1 mmHg), was distilled. After the oil had been dissolved in a toluene - petroleum ether mixture, upon cooling 5.9 g. (80.9%) of *N*-(3-phenoxy-2-hydroxypropyl)aniline (IX) crystallized, m. p. 60—62°C (lit, 61—63°C). A mixture of IX (5.0 g.), pyridine (30 g.), and acetic anhydride (40 g.) was allowed to stand for 1 day at room temperature. Pyridine and acetic anhydride were removed by distillation under reduced pressure, and the residue was recrystallized several times from ethanol to give 4.8 g. (71.4%) of VIa, m. p. 96—97°C.

Found: C, 69.82; H, 6.43; N, 4.26. Calcd. for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28%.

N, N-Bis(3-phenoxy-2-hydroxypropyl)aniline Diacetate (VIIIa).—To a boiling solution of 6.5 g. (0.02 mol.) of IX in 30 ml. of benzene was added drop by drop with stirring 4.5 g. (0.03 mol.) of phenyl glycidyl ether in 50 ml. of benzene. The mixture was then heated under reflux for an additional hour. After the benzene had been removed, the residue, without purification, was dissolved in pyridine - acetic anhydride mixture; the solution was then allowed to stand for 1 day. The

pyridine and acetic anhydride were removed by distillation under reduced pressure, and the residue was recrystallized several times from ethyl acetate to give 5.7 g. (59.7%) of VIIIa, m. p. 171—172°C.

Found: C, 70.29; H, 6.55; N, 3.00. Calcd. for $C_{28}H_{31}NO_6$: C, 70.42; H, 6.54; N, 2.93%.

3-Aryl-5-aryloxymethyl-2-oxazolidones.—The results of the reaction between acid amides and glycidyl ethers are listed in Tables II and III. Experimental examples will be given below.

A. The Reaction of α, α, α-Trichloroacetanilide with Phenyl Glycidyl Ether.—A mixture of 7.2 g. (0.03 mol.) of α, α, α-trichloroacetanilide, 4.5 g. (0.03 mol.) of phenyl glycidyl ether, and 0.1 g. of triethylenediamine was heated at 100°C for 2 hr. After cooling, the adduct was recrystallized from acetone to give 6.5 g. (80%) of 3-phenyl-5-phenoxymethyl-2-oxazolidone, m. p. 138—139°C. A mixed-melting-point determination with an authentic sample showed no depression.

B. The Reaction of α, α, α-Trifluoro-*p*-methylacetanilide with Phenyl Glycidyl Ether.—A mixture of 6.1 g. (0.03 mol.) of α, α, α-trifluoro-*p*-methylacetanilide, 4.5 g. (0.03 mol.) of phenyl glycidyl ether, and 0.1 g. of triethyl benzylammonium bromide was heated at 110°C for 2 hr. After cooling, the adduct was recrystallized from acetone to give 7.4 g. (87%) of 3-*p*-tolyl-5-phenoxymethyl-2-oxazolidone, m. p. 149—151°C. A mixed-melting-point determination with an authentic sample showed no depression.

C. The Reaction of α, α, α-Trichloroacetanilide with *p*-Methoxycarbonylphenyl Glycidyl Ether.—A mixture of 11.9 g. (0.05 mol.) of α, α, α-trichloroacetanilide, 10.4 g. (0.05 mol.) of *p*-methoxycarbonylphenyl glycidyl ether, and 0.2 g. of triethyl benzylammonium bromide was heated at 95°C for 4 hr. After cooling, the adduct was recrystallized from ethanol to give 12.8 g. (78%) of 3-phenyl-5-(*p*-methoxycarbonylphenoxymethyl)-2-oxazolidone, m. p. 144—146°C.

Found: C, 65.83; H, 5.31; N, 4.34. Calcd. for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.24; N, 4.28%.