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The Reaction of *N*-Acylurethans with Phenyl Glycidyl Ether Accompanying Acyl Migration

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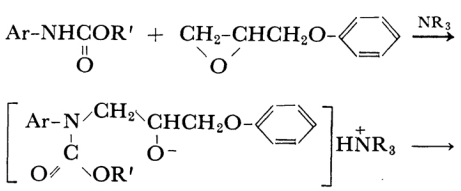
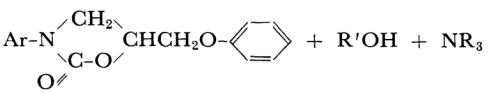
N-Acylethylurethans reacted with phenyl glycidyl ether to produce 3-acyl-5-phenoxymethyl-2-oxazolidones, 5-phenoxymethyl-2-oxazolidone and *N*-(2-acyloxy-3-phenoxypropyl)ethylurethans. The reaction mechanism involving acyl migration was discussed.

In an earlier paper[1] it has been shown that the addition condensation reaction between *N*-arylurethan and phenyl glycidyl ether occurs to form 2-oxazolidone in the presence of tertiary amines as catalysts:

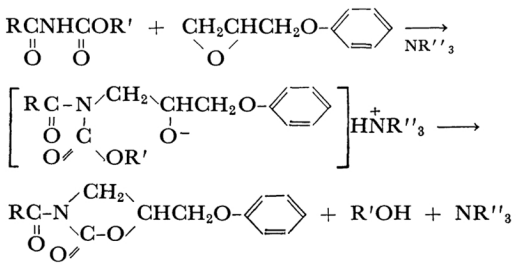




However, *N*-alkylurethans do not react with phenyl glycidyl ether. Further investigation of the reaction between *N*-(*p*-substituted phenyl)-urethans and phenyl glycidyl ether showed that electron-withdrawing substituents facilitated the reaction.

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

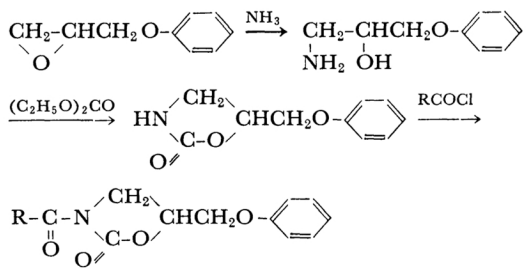
N-Acylurethans have been chosen in this study because of the electron-withdrawing ability of the acyl group. It is expected that 3-acyl-5-phenoxymethyl-2-oxazolidone will be obtained according to the following equation:



Results

The reaction of *N*-acylethylurethan with phenyl glycidyl ether was more complicated than had been expected. When this reaction was carried out at 70°C for 3—8 hr. in an organic solvent such as toluene or dimethylacetamide, using triethylenediamine as the catalyst, the products were 3-acyl-5-phenoxymethyl-2-oxazolidone and also 5-phenoxymethyl-2-oxazolidone. Moreover, *N*-(2-acyloxy-3-phenoxypropyl)ethylurethan, formed as the result of the N→O migration of the acyl group, was obtained. The reaction conditions and product ratios are listed in Table I.

The 3-acyl-5-phenoxymethyl-2-oxazolidones obtained by this reaction were identical with the authentic samples synthesized from acyl chlorides and 5-phenoxymethyl-2-oxazolidone. 5-Phenoxymethyl-2-oxazolidone was synthesized from 2-hydroxy-3-phenoxypropylamine and diethylcarbonate according to Homeyer's method:[2)]



The infrared spectra of 3-acyl-5-phenoxymethyl-2-oxazolidones showed two strong absorptions, at 1700 cm^{-1} and 1760 cm^{-1} which were assignable to the carbonyl groups in cyclic urethan and in the acyl substituent respectively. In the infrared spectrum of 5-phenoxymethyl-2-oxazolidone, the carbonyl absorption appeared at 1740 cm^{-1} and the NH-stretching at 3340 cm^{-1}, but no amide band at 1530 cm^{-1} (NH-deformation) was observed. Physical and analytical data on 3-acyl-5-phenoxymethyl-2-oxazolidones are listed in Table II.

N-(2-Acyloxy-3-phenoxypropyl)ethylurethans were characterized by elementary analysis, infrared spectra, and by a study of the saponification equivalent. These data are listed in Table III.

Discussion

The most likely reaction mechanism for the simultaneous formation of 3-acyl-5-phenoxymethyl-2-oxazolidone (IV) and *N*-(2-acyloxy-3-phenoxypropyl)ethylurethan (V) is the one which involves the common intermediate (III) formed by

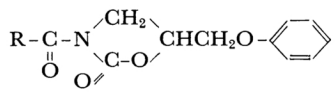
Table I. Reaction of *N*-acylethylurethans with phenyl glycidyl ether

Expt.[a)]	Moles of starting material	Solvent,	ml.	Reaction time hr.	Cat.,[b)] g.	Recovery %	Yield, % Acyl-oxazolidone	*N*-Unsubst.-oxazolidone	Acyloxy-urethan
A-1	0.04	Toluene	10	3	0.1	46	16	0	26
A-2	0.04	Toluene	10	3	0.2	24	44	5	12
A-3	0.04	Toluene	10	3	0.3	18	46	18	0
A-4	0.04	Toluene	10	8	0.2	23	47	16	0
A-5	0.04	DMAc	10	3	0.05	13	37	0	28
A-6	0.04	DMAc	10	3	0.1	5	42	7	20
A-7	0.04	DMAc	10	3	0.2	0	35	35	0
A-8	0.04	DMAc	10	8	0.2	0	46	45	0
P-1	0.08	Toluene	12	3	0.2	27	18	0	45
P-2	0.08	Toluene	12	8	0.2	19	19	0	41
P-3	0.04	DMAc	10	8	0.2	0	25	32	21
n-B-1	0.08	Toluene	15	8	0.2	26	18	0	43
n-B-2	0.04	DMAc	10	8	0.2	14	16	17	31
i-B-1	0.053	Toluene	10	8	0.2	7	24	2	47

a) Letters stand for *N*-substituent: A=acetyl, P=propionyl, B=butyryl.
b) Triethylenediamine.

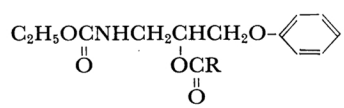
2) A. H. Homeyer, U. S. Pat. 2399118 (April 23, 1946).

Table II. Properties of 3-acyl-5-phenoxymethyl-2-oxazolidones



R	M. p., °C	Formula	Anal., % Calcd. / Found C	H	N	$\nu_{C=O}$, cm^{-1}	
CH_3	114.5—115.5	$C_{12}H_{13}NO_4$	61.27 61.22	5.57 5.50	5.96 5.89	1700	1760
C_2H_5	122—124	$C_{13}H_{15}NO_4$	62.64 62.35	6.07 5.90	5.62 5.73	1710	1760
$CH_3(CH_2)_2$	77— 78	$C_{14}H_{17}NO_4$	63.86 63.57	6.51 6.47	5.32 5.07	1700	1760
$(CH_3)_2CH$	99—101	$C_{14}H_{17}NO_4$	63.86 64.16	6.51 6.56	5.32 5.30	1690	1780

Table III. Properties of *N*-(2-acyloxy-3-phenoxypropyl)ethylurethans



R	B. p., °C/mmHg	Formula	Mol. wt.	Saponification equivalent	Anal., % Calcd. / Found C	H	N	$\nu_{C=O}$, cm^{-1}	
CH_3	147—148/0.03	$C_{14}H_{19}NO_5$	281	281	59.77 59.88	6.81 6.57	4.98 4.97	1730	1700
C_2H_5	150—153/0.05	$C_{15}H_{21}NO_5$	295	293	61.00 60.93	7.17 7.21	4.74 4.75	1720 (broad)	
$CH_3(CH_2)_2$	165—168/0.15	$C_{16}H_{23}NO_5$	309	311	62.12 62.30	7.49 7.41	4.53 4.51	1730	1700
$(CH_3)_2CH$	150—153/0.04	$C_{16}H_{23}NO_5$	309	307	62.12 62.79	7.49 7.30	4.53 4.30	1730	1700

the addition reaction of *N*-acylurethan (I) to phenyl glycidyl ether (II), as is depicted in Chart 1. The alkoxide anion in III can attack the carbonyl carbon either in the amide or urethan group intramolecularly. If the anion attacks the urethan carbonyl to cleave the acyl-oxygen linkage, IV and the ethoxide ion will be formed, while the attack on the amide carbonyl, followed by acyl-nitrogen cleavage, will result in the formation of V. The 5-phenoxymethyl-2-oxazolidone (VII) is considered to have resulted either from IV or V by the reaction of the ethoxide anion formed from III in the course of the formation of IV. The presence of ethanol and ethyl acetate was detected by the gas chromatographic analysis of the reaction mixture of I and II. As the ethoxide anion may possibly abstract the proton from $\overset{+}{H}N<$ to form ethanol, it cannot be expected that all of the ethoxide anions will effect the conversion of IV or V to VII.

When 3-acetyl-5-phenoxymethyl-2-oxazolidone (IVa) was treated with ethanol and sodium ethoxide in toluene, VII was obtained. On the contrary, no reaction occurred when IVa was treated with ethanol in the presence of triethylenediamine instead of sodium ethoxide. VII was also obtained by the hydrolysis of V with alcoholic sodium hydroxide. However, no change in the infrared spectrum of the solution of V in toluene was recognized after it had been heated for 8 hr. in the presence of triethylenediamine. The formation of VII, rather than of *N*-(2-hydroxy-3-phenoxypropyl)ethylurethan, from V by hydrolysis is explained by the reaction scheme as being through the intermediate VI, just as that of IV from I and II proceeds through III.

The phenomenon of acyl migration in 2-aminoethanol derivatives and in similar compounds is well known, and reaction mechanisms have been proposed by many authors.[3-6] According to these authors, acyl migrations are reversible and the N→O migration proceeds in acidic media, whereas the O→N migration proceeds in basic media. In addition, when the amino group is acylated after the N→O migration has taken place, no more reverse migration of acyl group (O→N) proceeds, even when it is treated with alkali.

3) L. H. Welsh, *J. Am. Chem. Soc.*, **69**, 128 (1947).
4) A. P. Phillips and R. Baltzly, ibid., **69**, 200 (1947).
5) L. H. Welsh, ibid., **71**, 3500 (1949).
6) G. E. McCasland, ibid., **73**, 2295 (1951).

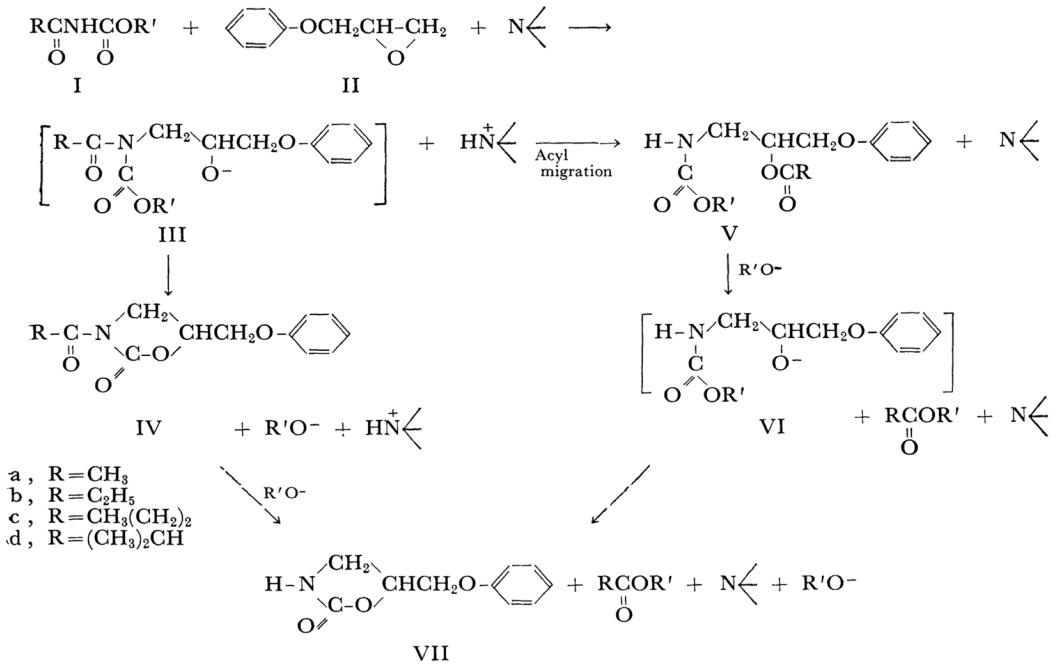
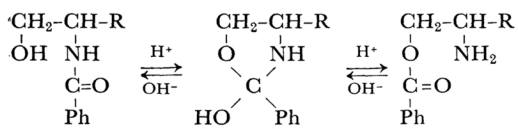


Chart 1



In the reaction of I with II, the N→O migration proceeded in basic media. The reverse migration of the acyl group, from V to III, was excluded, because prolonged reactions did not result in a decrease in V nor in an increase in IV, as is shown in Experiments P-1 and P-2. The change in the yield of V in Experiments A-3 and A-5 is the result of the formation of VII from V. The fact that the infrared spectrum of the solution of V in toluene did not change after it had been heated for 8 hr. also indicates that no migration from V to III proceeds. These experimental results may be explained by the difference in basicity between nitrogen and oxygen atoms.

In the reaction of epoxides with nucleophiles, the latter may attack either of the two epoxide-ring carbon atoms, leading to $-CH_2-O$ or $>CH-O$ fission. These two routes are usually referred to as "normal" and "abnormal" ring-opening respectively. In the reaction of I with II, normal opening was shown by NMR spectral study to occur. As Table IV shows, the methin protons of IV and VII give a signal at a field lower than that of 4-isopropyl-2-oxazolidone prepared from 2-hydroxy-1-isopropylethylamine and phosgene by 1.3 p. p. m. A similar observation about the effect of the neighboring atom on the chemical shift has been shown in the spectra of the $O-CH_3$ proton and the $N-CH_3$ proton, and it has been indicated that the $O-CH_3$ proton gives a signal at a field lower than that of the $N-CH_3$ proton by about 1 p. p. m., presumably because of the inductive effect of the neighboring oxygen atom.[7] The NMR spectra of IVa and VII were completely identical with those of 3-acetyl-5-phenoxymethyl-2-oxazolidone and 5-phenoxymethyl-2-oxazolidone prepared by Homeyer's method. Since the opening of the epoxide ring by ammonia is considered to be normal, the oxazolidones prepared by Homeyer's method are 5-substituted ones.

TABLE IV. NMR SPECTRAL DATA FOR METHIN PROTONS IN OXAZOLIDONE RINGS

2-Oxazolidones	δ, p. p. m.
3-Acetyl-5-phenoxymethyl	4.90
5-Phenoxymethyl	4.90
3-Phenyl-5-phenoxymethyl[a]	4.90
4-*i*-Propyl[b]	3.62

a) Prepared from *N*-phenylethylurethan and phenyl glycidyl ether.
b) Prepared from 2-hydroxy-1-isopropylethylamine.

Experimental

N-Acylurethans.—*N*-Acylethylurethans were prepared from acyl chlorides and ethyl carbamate as has

7) N. S. Bhacca and D. H. Williams, "Application of N. M. R. Spectra in Organic Chemistry," Holden-Day Co., London (1964), p. 39.

been described in the literature.[8] Their melting points and nitrogen analysis data were:

N-Acetyl, m. p. 77.5—78.5°C.

Found: N, 10.80. Calcd. for $C_5H_9NO_3$: N, 10.68%.

N-Propionyl, m. p. 78—81°C.

Found: N, 9.59. Calcd. for $C_6H_{11}NO_3$: N, 9.65%.

N-*n*-Butyryl, m. p. 63—65°C.

Found: N, 8.85. Calcd. for $C_7H_{13}NO_3$: N, 8.80%.

N-*i*-Butyryl, m. p. 100—101°C.

Found: N, 8.67. Calcd. for $C_7H_{13}NO_3$: N, 8.80%.

The Reaction of *N*-Acylethylurethan and Phenyl Glycidyl Ether.—A typical procedure (A-2) was as follows. A mixture of 5.24 g. (0.04 mol.) of *N*-acetylethylurethan and 6.00 g. (0.04 mol.) of phenyl glycidyl ether in 10 ml. of toluene was heated to 70°C, and then 0.2 g. of triethylenediamine was added to the mixture. The mixture was refluxed at 70°C for 3 hr. under reduced pressure. After the solvent had been removed in a vacuum, the reaction mixture was distilled at 0.4 mmHg. *N*-Acetylethylurethan was recovered by sublimation at first, and then phenyl glycidyl ether was distilled at 71—74°C. A fraction boiling at 160—190°C at 0.1 mmHg was collected (5.88 g.). This was a pale yellow, viscous liquid consisting of a mixture of 3-acetyl-5-phenoxymethyl-2-oxazolidone, 5-phenoxymethyl-2-oxazolidone and *N*-(2-acetoxy-3-phenoxypropyl)ethylurethan; it crystallized partially after it had stood overnight. It was treated with 30 ml. of cold ether and filtered to remove liquid *N*-(2-acetoxy-3-phenoxypropyl)ethylurethan. The crystalline part weighed 4.24 g. A portion of 2.00 g. of the crystals was treated with 200 ml. of boiling cyclohexane and filtered in hot to extract 3-acetyl-5-phenoxymethyl-2-oxazolidone. The remaining crystals were treated by the same method four times using each 200 ml. of cyclohexane. Finally, 0.15 g. of 5-phenoxymethyl-2-oxazolidone was obtained as an insoluble material which was proved to be free from 3-acetyl-5-phenoxymethyl-2-oxazolidone on the basis of infrared spectral analysis. It was further purified by recrystallization from 1500 ml. of cyclohexane; m. p. 121—122°C.

Found: C, 62.43; H, 5.52; N, 7.40. Calcd. for $C_{10}H_{11}NO_3$: C, 62.16; H, 5.74; N, 7.25%.

Five filtrates obtained from the above treatments were combined and evaporated. The residue (1.75 g.) was recrystallized from a mixture of 500 ml. of ether and 10 ml. of acetone to give 3-acetyl-5-phenoxymethyl-2-oxazolidone, m. p. 114.5—115.5°C.

Found: C, 61.22; H, 5.50; N, 5.89. Calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.96%.

A liquid portion of the *N*-(2-acetoxy-3-phenoxypropyl)ethylurethan obtained at the beginning of this fractionation procedure was evaporated to give 1.29 g. of *N*-(2-acetoxy-3-phenoxypropyl)ethylurethan. Distillation gave a pure product, b. p. 147—148°C at 0.03 mmHg.

Found: C, 59.88; H, 6.57; N, 4.97. Calcd. for $C_{14}H_{19}NO_5$: C, 59.77; H, 6.81; N, 4.98%.

The yields of 3-acetyl-5-phenoxymethyl-2-oxazolidone, 5-phenoxymethyl-2-oxazolidone, and *N*-(2-acetoxy-3-phenoxypropyl)ethylurethan were 4.16 g. (44%), 0.35 g. (5%), and 1.37 g. (12%) respectively, on the basis of the above-mentioned fraction collected at 160—190°C at 0.1 mmHg.

The Saponification Equivalent of *N*-(2-Actloxy-3-phenoxypropyl)ethylurethan.—A typical procedure was as follows. Into a 100-ml. Erlenmeyer flask, 0.7465 g. of *N*-(2-acetoxy-3-phenoxypropyl)ethylurethan was taken. Fifteen milliliters of a 0.5 N alcoholic sodium hydroxide solution was then added to the flask. The solution was allowed to stand at room temperature for 1.5 hr., and then it was warmed at 40°C for 5 min. The excess alkali was titrated by means of 0.2 N hydrochloric acid. The saponification equivalent was found from the amount of alkali consumed to be 281 (calcd. 281).

The hydrolyzed mixture was evaporated under reduced pressure, and then the residue was recrystallized from ether to give white crystalline 5-phenoxymethyl-2-oxazolidone.

The Hydrolysis of 3-Acetyl-5-phenoxymethyl-2-oxazolidone.—A solution of 0.820 g. of 3-acetyl-5-phenoxymethyl-2-oxazolidone in 20 ml. of 0.5 N alcoholic sodium hydroxide was allowed to stand for 8 hr. at room temperature. The mixture was then evaporated under reduced pressure, and the residual solid was washed with 1 ml. of water to give 0.376 g. (56%) of 5-phenoxymethyl-2-oxazolidone.

The Acylation of 5-Phenoxymethyl-2-oxazolidone.—A typical procedure was as follows. A mixture of 1.93 g. (0.01 mol.) of 5-phenoxymethyl-2-oxazolidone and 1.1 g. (0.011 mol.) of triethylamine in 50 ml. of benzene was heated to 80°C. Into the mixture, a solution of 1.10 g. (0.01 mol.) of propionyl chloride in 20 ml. of benzene was added, drop by drop, over a 10-min. period. As the reaction proceeded, triethylamine hydrochloride precipitated. The mixture was refluxed for 2 hr. and filtered in hot to remove triethylamine hydrochloride. The filtrate was evaporated under reduced pressure, and the residual white solid was washed with 5 ml. of water to remove the triethylamine hydrochloride completely. The crude product weighed 2.67 g. (100%). It was distilled at 0.04 mmHg, and the fraction boiling at 162—165°C was collected to give 1.95 g. (74%) of 3-propionyl-5-phenoxymethyl-2-oxazolidone. After the recrystallization from diethyl ether had been repeated, pure 3-propionyl-5-phenoxymethyl-2-oxazolidone was obtained; m. p. 122—124°C.

Found: C, 62.95; H, 5.66; N, 5.67. Calcd. for $C_{13}H_{15}NO_4$: C, 62.64; H, 6.07; N, 5.62%.

8) D. Ben-Ishai and E. Katchalski, *J. Org. Chem.*, **16**, 1025 (1951).