Stereochemistry of the Isomerization of *N*-Acyl-2,3-Disubstituted Aziridines to Δ^2-Oxazolines

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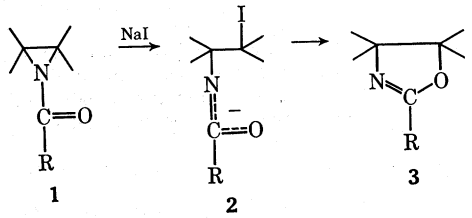
The iodide ion catalyzed isomerization of *cis*- and *trans*-1-acetyl and 1-aroyl-2,3-disubstituted aziridines to Δ^2-oxazolines has been studied. The rearrangement is stereoselective, the selectivity being greater with *trans*-aziridines than with *cis*-aziridines. The former yield 90–95% *trans*- and 10–5% *cis*-Δ^2-oxazolines while the latter give 40–90% *cis* and 60–10% *trans*. The selectivity of isomerization for *cis*-1-aroylaziridines was found to vary with the iodide ion concentration and the solvent system employed while the ratio of Δ^2-oxazolines formed from the corresponding *trans*-aziridines was unaffected. Using tetrabutylammonium iodide as the isomerization catalyst also affected the Δ^2-oxazoline isomer distribution. The stereochemical outcome of this reaction was found to be insensitive to the size of the 2,3-dialkyl substituents and to resonance effects. The ratio of isomers formed was determined by glpc, while stereochemical configurations were elucidated by means of nmr spectroscopy.

The rearrangement of *N*-acylaziridines (**1**) to the isomeric 2-aryl- or 2-alkyl-Δ^2-oxazoline ring system (**3**) by nucleophiles such as iodide ion and thiocyanate ion has been the subject of a number of studies.[2–6] The mechanism of the iodide-catalyzed isomerization has



R = aryl or alkyl

been postulated as occurring by attack of the nucleophile on a carbon atom of the aziridine ring to produce

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(1) Agricultural Research Service, U. S. Department of Agriculture.

(2) H. W. Heine, *Angew. Chem. Int. Ed. Engl.*, **1**, 528 (1962).

(3) P. Thyrum and A. R. Day, *J. Med. Chem.*, **8**, 107 (1965).

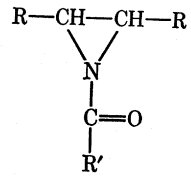
(4) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 3828 (1965).

(5) P. E. Fanta and E. N. Walsh, *J. Org. Chem.*, **31**, 59 (1966).

(6) P. E. Fanta, R. J. Smat, and J. R. Krikau, *J. Heterocycl. Chem.*, **5**, 419 (1968).

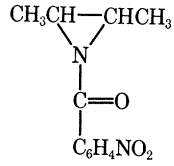
TABLE I

N-ACYLAZIRIDINES



Compd	Stereochemistry	R	R′	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7a	cis	C_2H_5	C_6H_5	76.81	8.43	6.89	76.77	8.51	6.88
8a	trans	C_2H_5	C_6H_5	76.81	8.43	6.89	76.97	8 41	6.81
7b	cis	C_8H_{17}	C_6H_5	80.80	11.12	3.77	80.72	11.11	3.76
8b	trans	C_8H_{17}	C_6H_5	80.80	11.12	3.77	80.60	11.07	3.70
7c	cis	C_2H_5	CH_3	68.04	10.71	9.92	68.17	10.63	9.82
8c	trans	C_2H_5	CH_3	68.04	10.71	9.92	68.12	10.73	9.83
7d	cis	C_2H_5	p-$NO_2C_6H_4$–	62.89	6.50	11.28	62.87	6.53	11.42
7e	cis	C_8H_{17}	p-NO_2-C_6H_4–	72.08	9.68	6.72	71.93	9.52	6.66
7f	cis	C_8H_{17}	CH_3	77.61	12.70	4.53	77.65	12.77	4.50

an intermediate *N*-2-iodoalkyl amido ion (**2**) which subsequently cyclizes to the oxazoline.[2,7] Such a mechanism predicts that rearrangement of *N*-acyl-2,3-disubstituted aziridines to 4,5-disubstituted Δ^2-oxazolines should be a stereospecific process.[7] Indeed, a stereospecific rearrangement has been observed for the iodide-catalyzed isomerization of *N*-*p*-nitrobenzoyl-2,3-dimethylaziridine[7] (**4**) and *N*-*p*-nitrobenzoylcyclohexylimine (**5a**).[8] In contrast, *N*-benzoylcyclohexylimine (**5b**) did not give the expected Δ^2-oxazoline isomer but *trans*-2-iodocyclohexylbenzamide (**6**) as the sole reaction product.[6,8]



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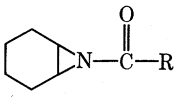
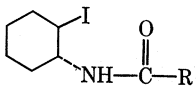


5a, R = $C_6H_4NO_2$
b, R = C_6H_5



6 R = C_6H_5

In view of the limited number of examples of stereospecific isomerizations of *N*-acyl-2,3-disubstituted aziridines to Δ^2-oxazolines and the failure of *N*-benzoylcyclohexylimine to isomerize to this ring structure the present investigation was undertaken. We have studied the iodide ion induced isomerization of a number of *N*-acyl-2,3-disubstituted aziridines with respect to the stereochemical course of this reaction.

Experimental Section

Nmr spectra were obtained on a Jeolco CH-60 spectrometer.[9] Chemical shifts are reported as δ (parts per million) relative to tetramethylsilane (TMS). The samples were run as 10% solutions in chloroform-*d*. Infrared spectra were obtained on a Perkin-Elmer Model 237 spectrometer. Glpc was carried out on a Hewlett–Packard Model 810 gas chromatograph. Silica gel H (Brinkmann) was used for thin layer analyses. Spots were detected by heat charring after spraying with 50% sulfuric acid. Melting points were determined in a capillary and are uncorrected unless otherwise noted.

Preparation and Purity of Aziridines.—The synthesis of the aziridines used in this study was carried out by the iodine isocyanate route.[10,11] Their purity was shown to be >99% by gas–liquid (glpc) and thin layer chromatography (tlc) and by titration with perchloric acid.[12]

Preparation of 1-Aroylaziridines. General Procedure.—To a solution of the aziridine (1 equiv) and triethylamine (1.1 equiv) in benzene under an atmosphere of nitrogen gas was added a solution of the acid chloride (1 equiv) in benzene at 10–15°. The reaction mixture was stirred at ambient temperature for 1 hr, and then the triethylamine hydrochloride was filtered. The benzene filtrate was washed with dilute NaOH solution and water and dried, and the solvent was removed *in vacuo*.

N-**Benzoyl**-*cis*-**2,3-diethylaziridine** (**7a**).—The crude benzoylaziridine obtained from *cis*-2,3-diethylaziridine and benzoyl chloride was chromatographed on Florisil. Elution with hexane gave the pure aziridine as a colorless oil, $n^{25}D$ 1.5216, in 73% yield: ir (neat) 3090 and 3025 (w) aziridine (C–H stretching), 1670 (s) carbonyl, 1315 and 1290 (s) cm^{-1}. The nmr spectrum consisted of two multiplets centered at 7.55 ppm (aromatic, 5 H), multiplets at 2.45 ppm (ring C–H, 2 H) and 1.60 ppm (methylene 4 H), and a triplet at 1.05 ppm (methyl 6 H). Elemental analysis is reported in Table I.

N-**Benzoyl**-*trans*-**2,3-diethylaziridine** (**8a**).—Obtained from *trans*-2,3-diethylaziridine, the product was chromatographed on silica gel. Elution with 1% ether–benzene gave the aziridine as a colorless oil, $n^{25}D$ 1.5194, in 85% yield: ir (neat) 3095 and 3025 (w) aziridine, 1665 (s) carbonyl, and 1330 (s) cm^{-1}. Its nmr spectrum consisted of a multiplet centered at 7.60 ppm (aromatic, 5 H) and three multiplets centered at 2.40, 1.40, and 1.05 ppm in the ratio of 1:2:3.

N-*p*-**Nitrobenzoyl**-*cis*-**2,3-diethylaziridine** (**7d**).—Obtained from the reaction of *cis*-2,3-diethylaziridine and *p*-nitrobenzoyl chloride, the pure product after recrystallization from methanol had mp 74–76°, 65% yield: ir (KBr) 3090 (m), 1660 (s) carbonyl, 1515 and 1340 (s) nitro, 1315 and 720 (s) cm^{-1}. The nmr spectrum consisted of 3 multiplets centered at 8.35 (5 H), 2.65 (2 H), and 1.80 (4 H) ppm and a triplet at 1.15 (6 H) ppm.

N-**Benzoyl**-*cis*-**2,3-dioctylaziridine** (**7b**).—Obtained from the reaction of *cis*-2,3-dioctylaziridine[13] with benzoyl chloride, the crude product was chromatographed on Florisil. Elution with hexane gave the pure aziridine as a colorless oil, $n^{25}D$ 1.4940, in 85% yield: ir (neat) 3090 and 3025 (w) aziridine, 1675 (s) carbonyl, 1310 and 1280 (s) cm^{-1}. Its purity exceeded 99% as determined by tlc and ring titration.[12]

N-**Benzoyl**-*trans*-**2,3-dioctylaziridine** (**8b**).—This compound was obtained from *trans*-2,3-dioctylaziridine.[13] Chromatography on Florisil, followed by elution with hexane gave the pure *N*-benzoylaziridine as a colorless oil, $n^{25}D$ 1.4940, in 90% yield:

(7) H. W. Heine, D. C. King, and L. A. Portland, *J. Org. Chem.*, **31** 2662 (1966).

(8) P. E. Fanta and E. N. Walsh, *ibid.*, **30**, 3574 (1965).

(9) Mention of brand or firm names does not constitute an endorsement by the Department of Agriculture over others of a similar nature not mentioned.

(10) A. Hassner and C. Heathcock, *Tetrahedron*, **20**, 1037 (1964).

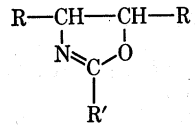
(11) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).

(12) G. Maerker, E. T. Haeberer, L. M. Gregory, and T. A. Foglia, *Anal. Chem.*, **41**, 1698 (1969).

(13) C. G. Gebelein, G. Swift, and D. Swern, *J. Org. Chem.*, **32**, 3314 (1967).

TABLE II

SUBSTITUTED Δ^2-OXAZOLINES



Compd	Stereochemistry	R	R′	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
9a	cis	C_2H_5	C_6H_5	52.78[a]	4.66[a]	12.96[a]	52.79[a]	4.45[a]	12.80[a]
10a	trans	C_2H_5	C_6H_5	52.78[a]	4.66[a]	12.96[a]	52.63[a]	4.44[a]	12.81[a]
9b	cis	C_8H_{17}	C_6H_5	80.80	11.12	3.77	80.92	11.29	3.64
10b	trans	C_8H_{17}	C_6H_5	43.30[a]	5.19[a]	14.42[a]	43.22[a]	5.25[a]	14.27[a]
9c	cis	C_2H_5	CH_3	45.41[b]	4.90[b]	15.13[b]	45.62[b]	4.77[b]	15.18[b]
10c	trans	C_2H_5	CH_3	62.89	6.50	11.28	62.71	6.57	11.42
9d	cis	C_2H_5	p-NO_2-C_6H_4–	62.89	6.50	11.28	62.94	6.47	11.15
10d	trans	C_2H_5	p-NO_2-C_6H_4–	72.08	9.68	6.72	71.93	9.81	6.53
9e	cis	C_8H_{17}	p-NO_2-C_6H_4–						
10e	trans	C_8H_{17}	p-NO_2-C_6H_4–	77.61	12.70	4.53	77.82	12.77	4.51
9f	cis	C_8H_{17}	CH_3						
10f	trans	C_8H_{17}	CH_3						

[a] Picrate salt monohydrate. [b] Picrate salt.

TABLE III

ISOMERIZATION OF N-AROYL-2,3-DIETHYLAZIRIDINES

Isomer	Δ^2-Oxazoline *cis*, %	Δ^2-Oxazoline *trans*, %	Solvent	Catalyst	Mole ratio, iodide:aziridine
cis-Benzoyl	53.1	46.9	Acetone	NaI	3.4:1
cis-Benzoyl	47.6	52.4	Acetone	NaI	5.0:1
cis-Benzoyl	75.0	25.0	Acetonitrile	NaI	5.0:1
cis-Benzoyl	57.6	42.4	Benzene	TBAI[a]	5.0:1
cis-Benzoyl	53.1	46.9	Acetone	TBAI	5.0:1
cis-Benzoyl	72.8	27.2	Acetonitrile	TBAI	5.0:1
cis-Benzoyl	78.8	21.2	2% water, acetone	NaI	5.0:1
cis-*p*-Nitrobenzoyl	58.5	41.5	Acetone	NaI	5.0:1
trans-Benzoyl	6.8	93.2	Acetone	NaI	3.4:1
trans-Benzoyl	7.2	92.8	Acetone	NaI	5.0:1

[a] Tetra-*n*-butylammonium iodide.

ir (neat) 3070 and 3015 (w) aziridine, 1670 (s) carbonyl, and 135 (s) cm^{-1}. Purity by tlc and by ring titration was >99%.

N-*p*-**Nitrobenozyl**-*cis*-**2,3-dioctylaziridine (7e)**.—The crude product from *cis*-2,3-dioctylaziridine and *p*-nitrobenzoyl chloride was chromatographed on Florisil. Elution with hexane gave the pure compound as a pale yellow oil, $n^{25}D$ 1.5070, in 81% yield: ir (neat) 3100 and 3050 (w), 1675 (s) carbonyl, 1525 and 1340 (s) nitro, 1300 (s), 1020, 870, and 850 (m) cm^{-1}. Its purity by tlc (methanol–ether–benzene, 1:13:86) and titration exceeded 99%.

N-**Acetyl**-*cis*-**2,3-diethylaziridine (7c)**.—The crude *N*-acetylaziridine obtained from *cis*-2,3-diethylaziridine and acetyl chloride was distilled: bp 40–41° (0.4 mm); $n^{25}D$ 1.4628; 93% yield; ir (neat) 2970 (s), 1690 (s) carbonyl, 1360 (m), 1290 and 1220 (s) cm^{-1}. The nmr spectrum showed a singlet (3 H) at 1.98 ppm, two multiplets centered at 2.28 (2 H) and 1.45 (4 H) ppm, and a triplet (6 H) centered at 1.05 ppm.

N-**Acetyl**-*trans*-**2,3-diethylaziridine (8c)**.—This compound was prepared from *trans*-2,3-diethylaziridine and acetyl chloride. The pure aziridine was obtained by distillation: bp 35° (0.25 mm); $n^{25}D$ 1.4575; 72% yield; ir (neat) 2960 (s), 1680 (s) carbonyl, 1365 (s), 1320 (s), and 1190 (s) cm^{-1}. The nmr spectrum showed a singlet (3 H) at 2.14 ppm and three multiplets centered at 2.18, 1.52, and 1.10 ppm in the ratio of 1:2:3.

N-**Acetyl**-*cis*-**2,3-dioctylaziridine (7f)**.—The crude product was obtained in nearly quantitative yield from the reaction of *cis*-2,3-dioctylaziridine and acetyl chloride. Chromatography on Florisil and elution with hexane gave the pure sample as a colorless oil: $n^{25}D$ 1.4545; 92% yield; ir (neat) 3080 and 3025 (w), 1690 (s) carbonyl, 1360, 1285, and 1215 (s) cm^{-1}. Its purity exceeded 99% by ring titration and tlc (methanol–ether–benzene, 3:13:84).

cis- **and** *trans*-**4,5-Diethyl-2-phenyl-Δ^2-oxazoline (9a and 10a)**.—A solution of *N*-benzoyl-*cis*-2,3-diethylaziridine (**7a**, 1 mmol) and sodium iodide (5 mmol) in 25 ml of dry acetone was heated at reflux for 16 hr. The solvent was removed *in vacuo*, and the solid residue was extracted with hexane. Removal of the hexane gave a clear oil in nearly quantitative yield. Tlc of this residue showed the presence of only one component (R_f 0.55, methanol–ether–benzene, 7:13:80, starting material R_f 0.70). The ir spectrum contained an intense band at 1660 cm^{-1} which is generally characteristic of Δ^2-oxazoline structures.[14] Glpc of this material proved it to be a mixture of two components (ratio 48:52). They were separated by preparative glpc employing an 8 ft × 1/2 in. stainless steel column packed with 10% Carbowax 20M on Diatoport S 60–80 mesh at 180° with a helium flow of 150 ml/min.

The faster eluting component was identified as *trans*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**10a**) on the basis of its nmr spectrum (see Discussion). Its ir spectrum (neat) displayed bands at 2960 (s), 1650 (s) C=N, 1490 (m), 1450, 1345 (s), 1075 (m), 1060 (s), 1025 (s), 940 (m), 775 (m), and 690 (s) cm^{-1}. The picrate salt of this isomer had mp 133.5–134.5°. Elemental analysis is reported in Table II.

The slower component was identified as *cis*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**9a**) in analogous fashion as the trans isomer. Its ir spectrum (neat) showed bands at 2960 (s), 1656 (s) C=N, 1490 (m), 1450 (s), 1370 (m), 1345 (s), 1075 (m), 1060, 1025 (s), 940, 775 (m), and 690 (s) cm^{-1}. The picrate salt of this isomer had mp 144–145.5°. Elemental analysis is reported in Table II.

The isomerization of *N*-benzoyl-*trans*-2,3-diethylaziridine (**8a**) was carried out in the manner previously described for **7a**. This result as well as those obtained from the isomerization of the cis isomer under varying solvent and catalysis systems is summarized in Table III.

(14) A. R. Katritsky, Ed., "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, p 218.

***cis*- and *trans*-4,5-Diethyl-2-methyl-Δ^2-oxazoline (9c and 10c).**—Isomerization of *N*-acetyl-*cis*-2,3-diethylaziridine (**7c**) to the isomeric Δ^2-oxazoline structure was effected in the same manner as the isomerization of the *N*-benzoyl derivative **7a**. The crude product was distilled to give a clear oil, bp 42° (2 mm), yield 77%. Tlc of the distillate indicated one component (R_f 0.35, methanol–ether–benzene, 7:13:80, starting material R_f 0.61). The ir spectrum had a strong band at 1670 cm^{-1}. Glpc of this product, however, showed it to be a mixture of two components in 1:3 ratio. They were separated by preparative glpc employing an 8 ft × 1/2 in. stainless steel column packed with 10% Apiezon-L on Diatoport S 60–80 mesh at 125°, He flow 100 ml/min.

The minor component was identified as *trans*-4,5-diethyl-2-methyl-Δ^2-oxazoline (**10c**) from its nmr spectrum (see Discussion). Its ir spectrum (neat) showed bands at 2960, 1670 (s) C=N, 1240 (m), 1225 and 950 (s) cm^{-1}. The picrate salt had mp 164–165°. Elemental analysis is reported in Table II.

The major component, *cis*-4,5-diethyl-2-methyl-Δ^2-oxazoline (**9c**), was also identified on the basis of its nmr spectrum. Its ir (neat) displayed bands at 2960, 1670 (s) C=N, 1380 (s), 1260 (m), 1225 and 950 (s) cm^{-1}. The picrate salt had mp 131–132°. Elemental analysis is reported in Table II.

Table IV summarizes the results obtained on the isomerization of *N*-acetyl-*cis*- and -*trans*-3,4-epiminohexane under varying reaction conditions.

TABLE IV

ISOMERIZATION OF *N*-ACETYL-2,3-DIETHYLAZIRIDINES

Isomer	Δ^2-Oxazoline *cis*, %	Δ^2-Oxazoline *trans*, %	Solvent	Catalyst	Mole ratio, iodide: aziridine
cis	81.2	18.8	Acetone	NaI	2.4:1
cis	75.2	24.8	Acetone	NaI	4.7:1
cis	73.5	26.5	Acetonitrile	NaI	4.7:1
cis	48.9	51.1	Benzene	TBAI	4.7:1
trans	7.8	92.2	Acetone	NaI	4.7:1

***cis*- and *trans*-4,5-Diethyl-2-*p*-nitrophenyl-Δ^2-oxazoline (9d and 10d).**—The crude isomerization product of *N*-*p*-nitrobenzoyl-*cis*-2,3-diethylaziridine (**7d**) was found to be homogeneous by tlc (R_f 0.54, methanol–ether–benzene, 1:13:86, starting aziridine R_f 0.71). Glpc analysis, however proved the presence of two components in the ratio 3:2. Separation of the isomers was accomplished on a 6 ft × 1/4 in. column packed with 15% OV-1 at 220°, He flow 60 ml/min.

The less polar compound, *trans*-4,5-diethyl-2-*p*-nitrophenyl-Δ^2-oxazoline (**10d**), was identified by comparison of its nmr spectrum with that of **10a**. The pure sample had mp 52–53°: ir (KBr) bands at 1640 (s) C=N, 1590 (s) C=C, 1155 and 1340 (s) NO_2, 1110, 1070 (s), 940, 850 (m), and 710 (s) cm^{-1}. Elemental analysis is reported in Table II.

The nmr spectrum of the more polar component established its structure as *cis*-4,5-diethyl-2-*p*-nitrophenyl-Δ^2-oxazoline (**9d**). The pure compound had mp 78.5–80°: ir (KBr) bands at 1635 (s) C=N, 1595 (s) C=C, 1520 and 1340 (s) NO_2, 1075 (s), 930, 850 (m), and 700 (s) cm^{-1}.

***cis*- and *trans*-4,5-Dioctyl-2-phenyl-Δ^2-oxazoline (9b and 10b).**—The crude isomerization product from *N*-benzoyl-*cis*-2,3-dioctylaziridine (**7b**) was chromatographed on a Florisil column. Elution with hexane gave the pure sample as a colorless oil, $n^{25}D$ 1.4943, in 92% yield. Tlc of this product indicated it to be homogeneous (R_f 0.58, methanol–ether–benzene, 1:13:86, starting material R_f 0.83). Its ir spectrum showed bands at 2830 (s), 1650 (s) C=N, 1080 (m), 1060 (s), 1025 (m), and 690 (s) cm^{-1}. Glpc of this oil on a 6 ft × 1/4 in. column packed with 10% Apiezon-L at 270°, He flow 60 ml/min, showed the presence of two components in ratio of 51:49. The two components were identified as the trans and cis isomers by comparison of their glpc retention times with authentic samples prepared by the thermal dehydration of the corresponding β-hydroxy amides.[15] Elemental analysis of the mixture is reported in Table II.

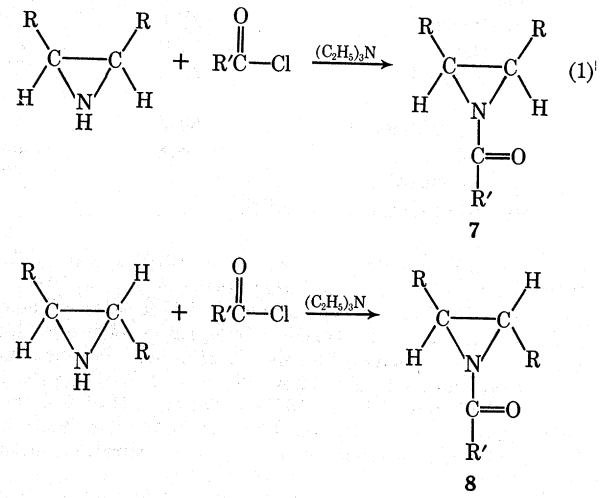
***cis*- and *trans*-4,5-Dioctyl-2-methyl-Δ^2-oxazoline (9f and 10f).**—Isomerization of *N*-acetyl-*cis*-2,3-dioctylaziridine (**7f**) was performed in the usual manner. The pure sample was obtained as a clear oil, $n^{27}D$ 1.4502, after chromatography on Florisil. Its ir spectrum (neat) showed absorption at 2960 (s), 1670 (s) C=N, 1385, 1375 (m), 1225 (s), 960 and 825 (m), cm^{-1}. Tlc showed this sample to be homogeneous (R_f 0.38, methanol–ether–benzene, 3:13:84, starting material R_f 0.58). Glpc of this oil on a 6 ft × 1/4 in. column packed with 10% Apiezon-L at 220°, He flow 60 ml/min, showed the presence of two components in ratio of 17:83. Identification as the trans and cis isomers was made by comparison of glpc retention times with authentic samples.[15] Elemental analysis of the mixture is reported in Table II.

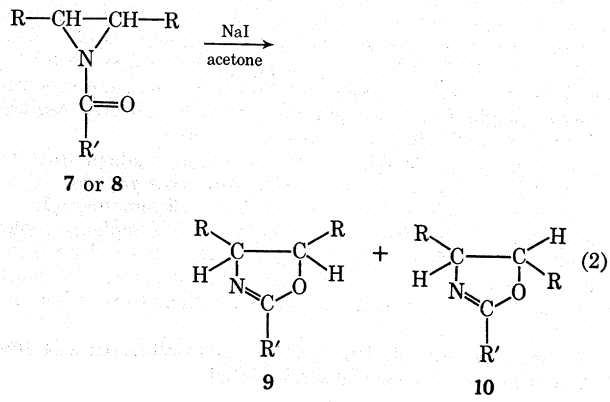
***cis*- and *trans*-4,5-Dioctyl-2-*p*-nitrophenyl-Δ^2-oxazoline (9e and 10e).**—The crude product obtained from the isomerization of *N*-*p*-nitrophenyl-*cis*-2,3-dioctylaziridine (**7e**) was chromatographed on silica gel. Elution with benzene gave the pure product as a pale yellow oil, $n^{27}D$ 1.5077, in 77% yield. The material was homogeneous by tlc (R_f 0.52, ether–benzene, 5:95, starting material R_f 0.72). Glpc analysis on a 2 ft × 1/4 in. OV-17 column at 275°, He flow 60 ml/min, showed the presence of two closely related compounds in approximately equal amounts. The mixture was judged to consist of equal parts of the two isomeric oxazolines **9e** and **10e** by virtue of its elemental analysis (see Table II) and its ir spectrum (neat): bands at 2960, 1645 (s) C=N, 1600 (m) C=C, 1540 and 1340 (s) NO_2, 1075, 1015, 870, 850, 755, and 700 (m) cm^{-1}.

(15) W. E. Parker, private communication.

Results and Discussion

The acylated aziridines selected for this study were prepared by the reaction of the appropriate *cis*- or *trans*-dialkylaziridine obtained *via* the iodine isocyanate procedure,[10,11] with an acyl chloride in the presence of triethylamine (eq 1). Treatment of the *N*-acylaziridines (**7** and **8**) with sodium iodide in refluxing acetone gave the corresponding 2-alkyl- or 2-aryl-4,5-dialkyl-Δ^2-oxazolines (**9** and **10**) in nearly quantitative yields as determined by tlc and ir (eq 2). Examination of the





rearrangement products by analytical gas–liquid chromatography (glpc) showed that they were mixtures of the two geometric isomers, **9** and **10**. Mixtures of lower homologs of **9** and **10** were separated by preparative glpc and identified by elemental analysis, ir, and nmr. Higher homolog mixtures could be separated by analytical but not by preparative glpc, and in these cases the structures of the combined isomers were confirmed by elemental analysis and ir. The assignment of the stereochemistry of **9** and **10** was made from the nmr spectra of individual compounds as detailed below. In all glpc separations the trans isomer **10** was the faster eluting component.

The acylated aziridines which were studied are listed in Table I, and the resulting substituted Δ^2-oxazolines are shown in Table II. The rearrangement of the isomeric aziridines occurs with essentially equal facility, but the stereoselectivity of this conversion differs considerably for the cis and trans isomers. It is apparent from the data presented in Tables III–V that more than 90% of the Δ^2-oxazolines obtained have the trans configuration when *N*-aroyl-*trans*-aziridines are treated with sodium iodide in acetone. Under the same conditions the corresponding *cis*-aziridines give nearly equal amounts of *cis*- and *trans*-Δ^2-oxazolines. For instance, *N*-benzoyl-*trans*-2,3-diethylaziridine (**8a**) forms *trans*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**10a**) and the corresponding cis isomer **9a** in a ratio of 93:7. On the other hand, *N*-benzoyl-*cis*-2,3-diethylaziridine (**7a**) forms the same two oxazolines (**10a** and **9a**) in the ratio of 52:48.

TABLE V

ISOMERIZATION OF *N*-ACYL-2,3-DIOCTYLAZIRIDINES

Compd	Δ^2-Oxazoline *cis*-, %	Δ^2-Oxazoline *trans*-, %	Solvent	Catalyst	Mole ratio, iodide: aziridine
cis-N-Benzoyl	51.0	49.0	Acetone	NaI	5.0:1
cis-N-Acetyl	83.0	17.0	Acetone	NaI	5.0:1
cis-p-Nitrobenzoyl	60[a]	40[a]	Acetone	NaI	5.0:1
trans-N-Benzoyl	4.4	95.6	Acetone	NaI	5.0:1

[a] Estimated by glpc.

Isomerization of *N*-acetyl-*cis*- and -*trans*-2,3-diethylaziridines (**7c** and **8c**) also gave mixtures of *cis*- and *trans*-Δ^2-oxazolines. Again, the *trans*-aziridine (**8c**) gave predominantly *trans*-Δ^2-oxazoline, the ratio of **10c** to **9c** being 92:8. On the other hand, the *cis*-aziridine (**7c**) gave mostly *cis*-oxazoline, with a **10c** to **9c** ratio of 20:80. It therefore appears that the *cis*-alkanoylaziridines show a greater degree of stereoselectivity than the *cis*-aroyl derivatives.

The nmr data upon which the configurations of the 2-phenyl- and 2-methyl-4,5-diethyl-Δ^2-oxazolines are based are shown in Table VI. *trans*-4,5-Diethyl-2-phenyl-Δ^2-oxazoline (**10a**) showed protons H_a and H_b as quartets (J = 6.5 Hz) centered at 4.22 and 3.78 ppm, respectively. Since the coupling constant between H_a and H_b is of the same order of magnitude as the methylene coupling with H_a and H_b, all protons appear as equivalent hydrogens. Accordingly, H_a and H_b are observed as quartets. The more polar component of the mixture, *cis*-4,5-diethyl-2-phenyl-Δ^2-oxazoline (**9a**), was also identified from analysis of its nmr spectrum (Table VI). In this isomer protons H_a and H_b are seen at 4.62 and 4.10 ppm, respectively, as double triplets owing to the coupling of H_a with H_b (J_{ab} = 8.5 Hz) and each line being further coupled to the adjacent methylene protons ($J_{ac} = J_{bc}$ = 6.5 Hz). The observed difference in chemical shift of protons H_a and H_b in the two isomers is ascribed to the shielding effect of the alkyl groups attached to the adjacent carbon atoms in the trans isomer. The assignment as a cis or trans structure is made on the basis of the magnitude of the observed coupling constant between protons H_a and H_b in the two isomers. The trans configuration is assigned to the isomer with J_{ab} = 6.5 Hz while the isomer with J_{ab} = 8.5 Hz is assigned the cis configuration. This assignment of configuration is made by analogy with what has been previously observed in other five-membered heterocyclic ring systems, namely that cis proton coupling is generally larger than trans proton coupling.[16,17]

Further comment on the nmr spectra of the Δ^2-oxazolines would seem in order in view of what has been previously reported by Nishiguchi, *et al.*[18] These authors have reported that for *cis*- and *trans*-4,5-dimethyl-2-anilino-Δ^2-oxazoline the methine protons H_a and H_b appear as quintets with J_{ab} = 6.0 Hz for both isomers. Similar nmr spectral patterns were also observed for H_a and H_b in the corresponding sulfur analogs, *cis*- and *trans*-4,5-dimethyl-2-anilino-Δ^2-thiazoline. In these compounds the methine coupling constants were reported as 6.5 Hz for the cis derivative and 6.0 Hz for the trans isomer. Comparison of these J values with those observed in the present investigation reveals an apparent discrepancy in the methine coupling constant of *cis*-Δ^2-oxazolines. The observed J values for cis coupling in the present study were found to be on the order of 8.5 to 9.0 Hz, in contrast to the 6.0 and 6.5 Hz values previously reported. The J values for trans coupling are found to be of the same magnitude in both studies, being on the order of 6.0–6.5 Hz. This disparity in the magnitude of cis proton coupling in 4,5-disubstituted Δ^2-oxazolines cannot be explained at the present time until further work has been carried out to establish the general value of cis methine coupling.

To determine if a substituent effect could alter the stereochemical course of this iodide catalyzed isomerization of *N*-aroylaziridines, it was deemed advantageous to study the isomerization of *p*-nitrobenzoyl-*cis*-2,3-diethylaziridine (**7d**). This compound is structurally similar to those studied by Heine which reportedly rearranged stereospecifically.[7] Examination of the crude isomerization product of **7d** by glpc however confirmed the presence of two components (Table III). These materials were isolated and found to be the cis and trans isomers of 2-*p*-nitrophenyl-4,5-diethyl-Δ^2-oxazoline (**9d** and **10d**) by ir and elemental analysis. The assignment of stereochemistry was made by analysis of protons H_a and H_b in their nmr spectra and from their mass spectral fragmentation patterns.[19]

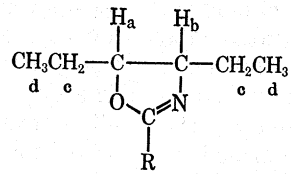
(16) T. A. Foglia and D. Swern, *J. Org. Chem.*, **34**, 1680 (1969).

(17) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, and references listed therein.

(18) T. Nishiguchi, H. Tochio, A. Nabeya, and Y. Iwakura, *J. Amer. Chem. Soc.*, **91**, 5835 (1969).

(19) S. Osman, C. J. Dooley, T. A. Foglia, and L. M. Gregory, *Org. Mass Spec.*, in press.

TABLE VI
NMR SPECTRA OF Δ^2-OXAZOLINES



Compd	H_a	H_b	H_c	H_n	R
trans-**10a** R = C_6H_5	4.22, quartet, $J_{ab} = J_{ac} = 6.5$ Hz	3.78, quartet, $J_{ba} = J_{bc} = 6.5$ Hz	1.64 (m)	0.98 (m)	7.38 (m) and 8.00 (m)
cis-**9a** R = C_6H_5	4.62, double triplet, $J_{ab} = 8.5$ Hz, $J_{ac} = 6.5$ Hz	4.10, double triplet, $J_{ba} = 8.5$ Hz, $J_{bc} = 6.5$ Hz	1.66 (m)	1.04 (t), $J_{dc} = 7.5$ Hz	7.44 (m) and 8.02 (m)
trans-**10c** R = CH_3	4.02, quartet, $J_{ab} = J_{ac} = 6.0$ Hz	3.54, quartet, $J_{ba} = J_{bc} = 6.0$ Hz	1.54 (m)	0.94 (t) $J = 7.5$ Hz	1.94
cis-**9c** R = CH_3	4.42, double triplet, $J_{ab} = 9.0$ Hz, $J_{ac} = 7.0$ Hz	3.90, double triplet, $J_{ba} = 9.0$ Hz, $J_{bc} = 7.0$ Hz	1.52 (m)	1.04 (m)	1.94

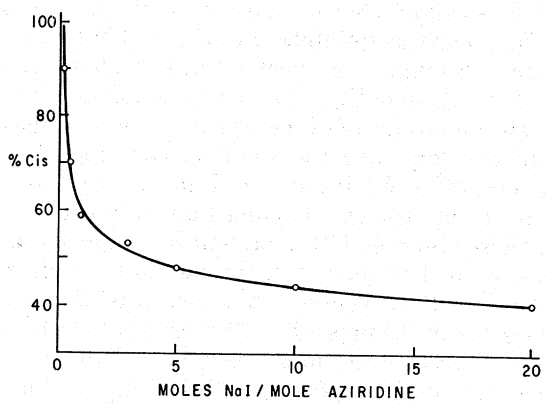


Figure 1.—Plot of per cent *cis*-oxazoline (**9a**) formed *vs.* mole ratio of NaI to aziridine (**7a**).

Verification that the above results were not caused by thermodynamic equilibration of the *cis*- and *trans*-oxazolines was obtained by subjecting the pure *cis*- and *trans*-2-*p*-nitrophenyl-Δ^2-oxazolines (**9d** and **10d**) to the reaction conditions. Glpc examination of the resulting reaction products confirmed the stability of the individual oxazoline isomers in that the presence of the other isomer could not be detected.

To determine whether the *cis*-:*trans*-oxazoline ratio could be affected by a change in the iodide ion concentration, the isomerization of *cis*-*N*-benzoyl-2,3-diethylaziridine (**7a**) with varying concentrations of iodide ion was studied. As can be seen from Figure 1 a pronounced change in the *cis*-:*trans*-oxazoline ratio was observed. At very high concentrations of iodide ion the amount of *cis*-oxazoline (**9a**) appears to approach a level of about 40%, while at very low concentrations of iodide ion the amount of *cis*-oxazoline (**9a**) formed increases asymptotically until nearly total selectivity is observed. As anticipated, it was found that as the iodide ion concentration decreased the rate of isomerization also decreased. For instance, at an iodide concentration of 0.1 mol–1.0 mol of aziridine less than 50% of the starting aziridine was isomerized after 60 hr of reaction. From the above data it can be concluded that the concentration of iodide ion not only affects the rate of isomerization, but more importantly that it can drastically alter the stereochemical outcome of the isomerization of *cis*-*N*-aroylaziridines to the isomeric Δ^2-oxazoline derivatives.

In order to determine whether the size of the alkyl substituents on the aziridine ring in any way influenced the stereoselectivity of the isomerization, the reactions of *N*-acyl-*cis*- and -*trans*-2,3-dioctylaziridine with iodide ion were investigated. As observed for the 2,3-diethylaziridine derivatives isomerization of *N*-phenyl-*cis*-2,3-dioctylaziridine (**7b**) gave a mixture of two components which were identified as the *trans*- and *cis*-4,5-dioctyl-2-phenyl-Δ^2-oxazoline isomers (**10b** and **9b**). The structural assignments were made on the basis of their glpc retention times (trans isomers less polar than cis isomers), elemental analysis, and mass spectral fragmentation data.[19] Isomerization of the trans isomer **8b** also gave a mixture of the two Δ^2-oxazolines, but as for the lower homolog a larger degree of stereoselectivity was observed (Table V). Also studied was the isomerization of *N*-acetyl- and *N*-*p*-nitrobenzoyl-*cis*-2,3-dioctylaziridine (**7f** and **7e**). The results obtained from the isomerization of these derivatives were comparable with the data obtained from the diethyl derivatives. The conclusion to be drawn from the above experiments is that the size of the alkyl substituent on the aziridine ring appears to have little if any effect in altering the stereochemical course of the iodide ion catalyzed isomerization of 2,3-dialkyl-*N*-acylaziridines to the isomeric Δ^2-oxazoline derivatives.

In order to determine whether solvent effects could be observed, the isomerization of the *N*-benzoyl-2,3-diethylaziridines (**7a** and **8a**) was repeated in acetonitrile and in acetone containing 2% water. No change was observed in the rearrangement of the *trans*-aziridine (**8a**), but for the cis isomer **7a** the change in solvent caused an increase in the amount of *cis*-oxazoline (**9a**) from 48% to 75–79% (see Table III). Increasing the water content in acetone further, however, had no addi-

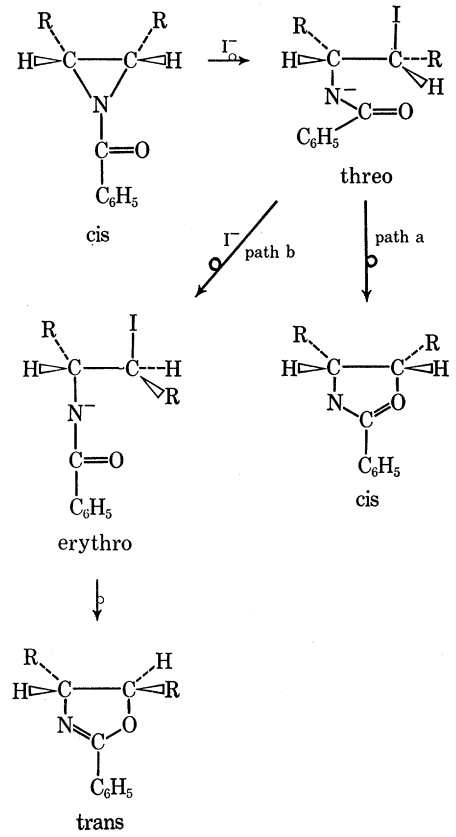
tional effect on the isomer distribution. For *N*-acetyl-*cis*-3,4-epiminohexane (**7c**) no change in isomer distribution was observed in going from acetone to acetonitrile solvent. The effect of water on the *N*-acetyl isomers could not be determined because of the propensity of 2-methyl-4,5-diethyl-Δ^2-oxazolines to hydrolyze.

Tetra-*n*-butylammonium iodide (TBAI), a catalyst which has been used previously in the rearrangement of aziridines to Δ^2-oxazolines,[20] was tested as an alternate source of iodide in acetone, acetonitrile, and benzene solution. TBAI and sodium iodide give similar results when applied to *N*-benzoyl-*cis*-2,3-diethylaziridine (**7a**) and to *N*-acetyl-*cis*-2,3-diethylaziridine (**7c**) in either acetone or acetonitrile solution. However, reaction of TBAI in benzene with acylated *cis*-aziridines results in a loss of selectivity in that a 1:1 mixture of *cis*- and *trans*-oxazolines is formed.

A mechanism which accounts for the lack of stereospecificity in the iodide ion catalyzed isomerization of *N*-acylaziridines, and which rationalizes the greater stereoselectivity observed in the rearrangement of the *trans*-aziridines than the *cis*-aziridines, is shown in Scheme I, using a *cis*-*N*-benzoylaziridine as a prototype. The initial step involves attack of the nucleophile on one of the carbon atoms of the aziridine ring with inversion of configuration to produce an intermediate *threo*-*N*-2-iodoalkylbenzamido ion. This ambident ion can now recyclize by a second nucleophilic inversion on the carbon atom bearing iodine to the *cis*-Δ^2-oxazoline structure (path a). An alternative reaction pathway for this threo intermediate, however, is for it to undergo an identity reaction (SN2) with a second iodide ion to give the diastereomeric *erythro*-*N*-2-iodoalkylbenzamido ion (path b). The so-produced erythro intermediate can then cyclize to the isomeric *trans*-Δ^2-oxazoline. This proposed interconversion of threo–erythro isomers by various nucleophiles has been previously observed in other reaction processes.[6,10,16]

The lower stereoselectivity observed in the iodide catalyzed isomerization of *cis*-2,3-dialkyl-substituted *N*-acylaziridines can be attributed to a higher degree of crowding of alkyl groups in the intermediate *threo*-*N*-2-iodoalkylbenzamido ion in approaching the transition state leading to Δ^2-oxazoline formation (trans–anti parallel arrangement of the iodine and benzamido group). Thus in the intermediate, *threo*-*N*-2-iodoalkylbenzamido ions, the identity reaction appears to become more competitive with ring closure than in the corresponding erythro isomers.

SCHEME I



Registry No.—**7a,** 25942-96-5; **7b,** 25942-98-7; **7c,** 25942-99-8; **7d,** 25943-00-4; **7e,** 25943-01-5; **7f,** 25943-02-6; **8a,** 25942-97-6; **8b,** 25943-03-7; **8c,** 25943-04-8; **9a,** 25943-05-9; **9a** (picrate), 25943-06-0; **9b,** 26015-58-7; **9c,** 25943-07-1; **9c** (picrate), 26015-57-6; **9d,** 25943-08-2; **9e,** 25943-09-3; **9f,** 25943-10-6; **10a,** 25943-11-7; **10a** (picrate), 26015-59-8; **10b,** 25943-12-8; **10c,** 25943-13-9; **10c** (picrate), 25943-14-0; **10d,** 25943-15-1; **10e,** 25943-16-2; **10f,** 25943-17-3.

Acknowledgment.—The authors would like to thank Mrs. M. T. Lukasewycz and Mrs. Annette Kravitz for performing the carbon, hydrogen, and nitrogen analyses.

(20) D. A. Tomalia, N. D. Ojha, and B. P. Thill, *J. Org. Chem.*, **34**, 1400 (1969).