Solvolytic Ring-opening Reacions of *gem*-Dichloroaziridines in the Presence of Sulfuric Acid

Manabu Senō, Shinsaku Shiraishi, Yukio Suzuki, and Teruzo Asahara
Institute of Industrial Science, University of Tokyo, Roppongi 7-22, Minato-ku, Tokyo 106

(Received July 1, 1975)

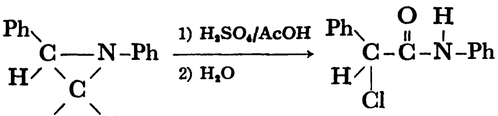
Solvolytic ring-opening reactions of *gem*-dichloroaziridines in the presence of sulfuric acid were investigated. The reaction products from 1-aryl-2,2-dichloro-3-phenylaziridines varied with the kind of substituent at 3-position of the aziridine ring. 2,2-Dichloro-1,3-diphenylaziridine gave α-chloro-α-phenylacetanilide, 2,2-dichloro-3-methyl-3-phenyl-1-(*m*-tolyl)aziridine gave *N*-(*m*-tolyl)atropamide and 2,2-dichloro-1,3,3-triphenylaziridine gave 3,3-diphenyloxindole. 1-Benzyl-2,2-dichloro-3,3-diphenylaziridine and 2,2-dichloro-1-phenethyl-3,3-diphenylaziridine gave 4,4-diphenyl-1,2,3,4-tetrahydroisoquinoline-3-one and 1,1-diphenyl-1,2,3,4,5-pentahydro-3-benzazepine-2-one, respectively. It was found that the substituent on C^3-carbon determines the mode of reaction.

gem-Dichloroaziridines have been prepared by various methods,[1-8] their reactivities being examined for hydrolysis,[1,2,3,6,8] isomerization[2,3] and aminolysis.[8] Ichimura and Ohta reported on the preparation of aromatic ketenimines from the reaction of 1,3,3-triaryl-2,2-dichloroaziridines with sodium iodide.[2] Klamann *et al.* observed that 1-(β-chloroethyl)-3,3-diphenyloxindole was produced by heating benzophenoneanil with chloroform and ethylene oxide in the presence of tetraethylammonium bromide, the reaction proceeding *via* the formation of 1,3,3-triaryl-2,2-dichloroaziridine.[7] On the other hand, Petyunin synthesized various lactams from *N*-aryl-α,α-diaryl-α-hydroxyacetamide in acetic acid in the presence of sulfuric acid.[9,10,11] These reports stimulated us to investigate in detail the reactivities of *gem*-dichloroaziridines in the medium containing sulfuric acid. It was found in the course of this study that atropamide, oxindole, isoquinoline and benzazepine derivatives are obtainable in good yields from the reactions of *gem*-dichloroaziridines in the presence of sulfuric acid. The results and analysis of the reaction scheme are presented in the present paper.

Results and Discussion

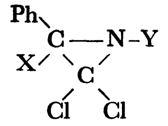
gem-Dichloroaziridines were prepared by addition of dichlorocarbene to the corresponding Schiff bases. Schiff bases were prepared by various methods Ph-CH=NPh was prepared from benzaldehyde and aniline, $Ph(CH_3)C=NAr$ from acetophenonediethylketal and *m*-toluidine, $Ph_2C=NPh$ from the reaction of sodium salt of aniline with benzophenone at 140—160 °C, and $Ph_2C=N(CH_2)_nPh$ (where $n=1,2$) by the reaction of $Ph_2C=O$ with $Ph(CH_2)_nNH_2$ at 150—180 °C in the presence of hydrobromic acid as a catalyst. *gem*-Dichloroaziridines prepared for the present investigation are listed in Table 1.

The *gem*-dichloroaziridines were treated with sulfuric acid in acetic acid. 2,2-Dichloro-1,3-diphenylaziridine (**1**) gave α-chloro-α-phenylacetanilide (**4**) in a 60% yield. The hydrolysis of **1** in a heterogeneous system in water affords **4** and the hydrolysis in a water–dioxane homogeneous system gives an equimolar mixture of **4** and α-hydroxy-α-phenylacetanilide.[3]



(**1**) (**4**)

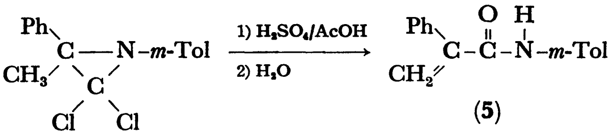
Table 1. *gem*-dichloroaziridines



Aziridine compd no.	X	Y	Mp, °C (lit.)
1	H	C_6H_5	97—98 (99—100)[3]
2[a]	CH_3	m-$CH_3C_6H_4$	65—66
3a	C_6H_5	C_6H_5	96—97 (97—98)[2]
3b	C_6H_5	$C_6H_5CH_2$	138—145[b] (136—137)[8]
3c[c]	C_6H_5	$C_6H_5(CH_2)_2$	80—81.5

a) Found: C, 65.45; H, 5.21; N, 4.79; Cl, 24.55%. Calcd for $C_{16}H_{15}NCl_2$: C, 65.75; H, 5.13; N, 4.79; Cl, 24.32%. b) This compound shows exothermic peaks at 135—140 °C and 148—153 °C in DTA curve. Found: C, 71.55; H, 4.74; N, 3.87%. Calcd for $C_{21}H_{17}NCl_2$: C, 71.19; H, 4.80, N, 3.95%. c) Found: C, 72.17; H, 5.19; N, 3.66%. Calcd for $C_{22}H_{19}NCl_2$: C, 71.74; H, 5.16; N, 3.80%.

2,2-Dichloro-3-methyl-3-phenyl-1-(*m*-tolyl)aziridine (**2**) gave *N*-(*m*-tolyl)atropamide (**5**) in a 61% yield. The product showed IR absorption at 1650 and 940 cm⁻¹ and NMR absorption (δ value) at 6.24 (singlet) and 5.70 (singlet) which comfirmed the existence of methylene group. The hydrolysis of **2** in water–dioxane (1: 3) mixture at reflux temperature for 1 h also gave the same product in a 62% yield. These reactions provide a novel convenient synthetic route to obtain atropamide. Meilahn *et al.* reported that 2,2-dichloro-3-ethyl-1,3-diphenylaziridines affords the hydrolysis product *via* a similar reaction.[8]

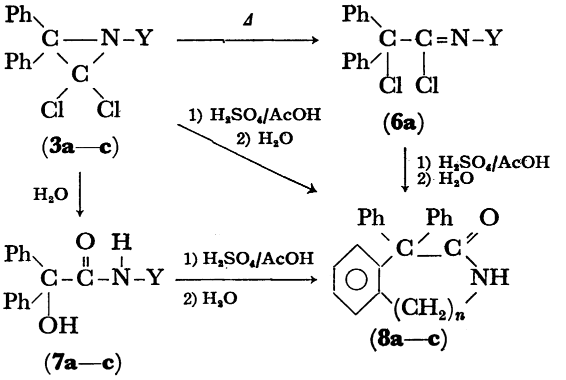


(**2**)

When concentrated sulfuric acid was added dropwise to a solution of 2,2-dichloro-1,3,3-triphenylaziridine (**3a**) in acetic acid, red coloration appeared instantaneously and disappeared shortly. This indicates the formation of carbonium ion as an intermediate. Concentrated sulfuric acid was added until no more coloration was observed. Working up the reaction mixture gave 3,3-diphenyloxindole (**8a**) in an 88% yield. On the other hand, by heating **3a** under anhydrous conditions, α-chloro-α,α-diphenyl-*N*-phenylacetimidoylchloride (**6a**) was obtained by thermal isomerization.* Compound (**6a**) thus prepared gave 3,3-diphenyloxindole (**8a**) quantitatively by treatment with sulfuric acid in acetic acid. Hydrolysis of **3a** in aqueous dioxane gave α-hydroxy-α,α-diphenylacetanilide (**7a**),[2] which also gave **8a** quantitatively by treatment with sulfuric acid.

In the presence of sulfuric acid as a catalyst, 1-benzyl-2,2-dichloro-3,3-diphenylaziridine (**3b**) gave 4,4-diphenyl-1,2,3,4-tetrahydroisoquinoline-3-one (**8b**) in a 99% yield. Hydrolysis of **3b** in aqueous dioxane gave *N*-benzylbenzilamide (**7b**),[8] which gave **8b** in an 80% yield by treatment with sulfuric acid. 2,2-Dichloro-1-phenethyl-3,3-diphenylaziridine (**3c**) gave 1,1-diphenyl-1,2,3,4,5-pentahydro-3-benzazepine-2-one (**8c**) in a 67% yield. Hydrolysis of **3c** gave *N*-phenethylbenzilamide (**7c**) in a 74% yield. Treatment of **7c** with sulfuric acid also gave **8c** in a 77% yield.

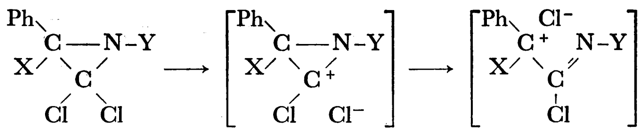
The reactions described above are summarized in the following scheme:



$Y=Ph(CH_2)_n$, a) $n=0$, b) $n=1$, c) $n=2$.

Petyunin *et al.* reported on the reaction from **7a** to **8a**[10-11] and Klamann *et al.* presented the reaction scheme to produce thermally oxindole from benzophenoneanil.[7] However, there is no report which gives the direct solvolytic rearrangement reactions of *gem*-dichloroaziridines to produce oxindole, isoquinoline derivatives and benzazepine derivatives. These reaction processes are rather moderate and give higher yields of products, as compared to the pyrolysis reaction at 150 °C reported by Klamann *et al.*

It was revealed from these experiments that the reaction proceeds through the cleavage of C³–N bond. The existence of **9** and **10** was proposed for intermediates in the ring-opening reaction of *gem*-dichloroaziridines, where the chloride ion shifts intramolecularly, following C³–N bond cleavage.[3] The nature of the intermediate (**10**) would be dependent on the substituent X.



(**9**) (**10**)

In the case of X=H, Cl^- is substantially bonding at C³-atom, and the product (**4**) is formed in both the reactions with H_2SO_4–AcOH and aqueous dioxane through α-chloro-*N*-phenylacetimidoylchloride, as reported by Brook *et al.*[3]

In the case of $X=CH_3$, the hydrolysis product is easily converted into compound (**5**) by an elimination pathway in both the reactions with H_2SO_4–AcOH and aqueous dioxane.

In the case of X=phenyl, the C³-carbonium ion is stabilized through the conjugation of adjacent phenyl groups and the counter Cl^- ion becomes more free. Thus, the attack of carbonium ion to benzene ring at *ortho* position or the displacement of Cl^- by OH^- becomes more feasible. Compounds (**8a**), (**8b**), and (**8c**) are produced by the reaction of parent dichloroaziridine with H_2SO_4–AcOH and *N*-aryl-α-hydroxy-α,α-diphenylacetamide (**7a**), (**7b**), or (**7c**) by the reaction in aqueous dioxane. The difference in the mode of reaction between **1** and **3** is considered to reflect the stability of benzyl cation as compared with that of benzhydryl cation.

Experimental

Preparation of N-*(1-Phenethylethylidene)*-m-*toluidine.* A mixture of 38.8 g (0.2 mol) of acetophenonediethylketal and 21.4 g (0.2 mol) of *m*-toluidine was heated at 80—100 °C for 7 h. The resulting solution was distilled under reduced pressure to give 35 g (84%) of *N*-(1-phenylethylidene)-*m*-toluidine as yellow liquid; bp 150 °C (3 mmHg); IR (KBr) 1634 cm⁻¹ (C=N); NMR ($CDCl_3$) δ (ppm) 6.3—8.1 (m, 9, aromatic), 2.30 (s, 3, CH_3-aromatic), 2.16 (s, 3, CH_3-C=N)

Preparation of N-*(Diphenylmethylidene)phenethylamine.* A mixture of 91 g (0.5 mol) of benzophenone, 60.5 g (0.5 mol) of phenethylamine and two drops of 2M hydrobromic acid was heated at 130—140 °C for 5 h under N_2 atmosphere. Distillation under reduced pressure gave 65 g (46%) of *N*-(diphenylmethylidene)phenethylamine as light yellow liquid; bp 190—195 °C (3 mmHg); IR (KBr) 1620 cm⁻¹ (C=N); NMR ($CDCl_3$) δ (ppm) 7.75—6.50 (m, 15, aromatic), 3.55 (t, 2, $-CH_2$-N=C–), 2.94 (t, 2, $-CH_2$-phenyl)

Preparation of 2,2-Dichloro-3-methyl-3-phenyl-1-(m-*tolyl)aziridine* (*2*). To a mixture of 28 g (0.25 mol) of potassium *t*-butoxide, 13 g (0.0625 mol) of *N*-(1-phenylethylidene)-*m*-toluidine and 250 ml of hexane, 30 g (0.25 mol) of chloroform was slowly added dropwise under dry N_2 atmosphere at 0—5 °C with vigorous stirring. The reaction mixture turned from yellow to brown. Stirring was continued for 2 h at 0—5 °C and then 2 h at room temperature. The solution was filtered and the residue was washed with hexane. The combined solution of the filtrate and the washing was then evaporated in *vacuo* to leave crystals, which gave 11.2 g (61%) of 2,2-dichloro-3-methyl-3-phenyl-1-(*m*-tolyl)aziridine as a colorless crystal by recrystalization from hexane–chloroform; mp 64—65 °C; IR (KBr) 1350 cm⁻¹ (symmetry stretching of aziridine ring); 840 cm⁻¹ (antisymmetry stretching of aziridine ring); NMR ($CDCl_3$) δ (ppm) 6.6—7.6 (m, 9, aromatic), 2.31 (s, 3, CH_3-

---

* Thermal isomerization of **3b** and **3c** was carried out by heating them in a solvent such as benzene, toluene or *p*-xylene. However, no product like **6a** could be isolated under the limited condition employed.

TABLE 2. REACTION PRODUCTS OF *gem*-DICHLOROAZIRIDINES IN THE PRESENCE OF SULFURIC ACID

Product	Mp, °C (lit,)	IR, cm^{-1} KBr disk	NMR, ppm in $CDCl_3$	Formula	Anal., % Found (Calcd) C	H	N
4	150—151 (146—148) a)	3300 (ν_{NH}) 1670 ($\nu_{C=O}$)	8.40 (broad, 1) 7.40 (m, 10) 5.45 (s, 1)	$C_{14}H_{12}NOCl$	68.41 (68.43)	4.81 (4.89)	5.65 (5.70)
5	134—135	3250 (ν_{NH}) 1650 ($\nu_{C=O}$) 1615 ($\nu_{C=C}$) 940 ($\nu_{=C-H}$)	7.40 (m, 9) 6.95 (broad, 1) 6.24 (s, 1) 5.70 (s, 1) 2.30 (s, 3)	$C_{16}H_{15}NO$	80.23 (81.01)	6.77 (6.33)	5.60 (5.91)
8a	237—238 (225—226) 10)	3200 (ν_{NH}) 1700 ($\nu_{C=O}$)	8.00 (broad, 1) 7.30 (m, 14)	$C_{20}H_{15}NO$	84.10 (84.21)	5.18 (5.26)	4.99 (4.91)
8b	280—300 (d) a)	3190 (ν_{NH}) 1680 ($\nu_{C=O}$)	8.90 (broad, 1) b) 6.70 (m, 14) 4.00 (s, 2)	$C_{21}H_{17}NO$	83.86 (84.28)	5.71 (5.69)	4.48 (4.68)
8c	199—200 (187—189) 11)	3300 (ν_{NH}) 1650 ($\nu_{C=O}$)	7.35 (m, 14) 4.70 (s, 1) 3.33 (q, 2) 2.60 (t, 2)	$C_{22}H_{19}NO$	84.36 (84.35)	6.32 (6.07)	4.47 (4.47)

a) Mp was not observed. It was found by DTA measurement that this compound decomposes at 280—300 °C.
b) Since this compound was not soluble in the usual organic solvents, NMR was measured in sulfuric acid.

aromatic), 1.73 (s, 3, CH_3-aziridine ring); UV (cyclohexane) λ_{max} 236 nm, ε_{max} 12900.

Preparation of 2,2-Dichloro-1-phenethyl-3,3-diphenylaziridine (3c). To a mechanically stirred mixture of 9 g (0.08 mol) of potassium *t*-butoxide, 8 g (0.028 mol) of *N*-(diphenylmethylidene)phenethylamine, 60 ml of benzene and 60 ml of hexane, 9.5 g (0.08 mol) of chloroform was slowly added dropwise under N_2 atmosphere at 0 °C. The mixture was stirred for 10 h at room temperature and then treated with active carbon for decoloration. After removal of the solid part from the solution by filtration, the filtrate was evaporated *in vacuo* to leave a crystal, which was recrystalized from hexane to leave a crystal, which was recrystalized from hexane to afford 4 g (39 %) of 2,2-dichloro-1-phenethyl-3,3-diphenylaziridine; mp 80—81 °C; IR (KBr) 1322 cm^{-1} (symmetry stretching of aziridine ring), 840 cm^{-1} (antisymmetry stretching of aziridine ring); NMR ($CDCl_3$) δ (ppm) 7.3 (m, 15, aromatic), 3.05 (q, 4, $-CH_2-CH_2-$).

Reaction of gem-*Dichloroaziridine in the Presence of Sulfuric Acid.* The general procedure is as follows: 20 ml of concd H_2SO_4 was slowly added dropwise to a solution of *gem*-dichloroaziridine (0.006 mol) in 20 ml of glacial acetic acid. The solution was heated at 60 °C for 30 min. It was poured into 80 ml of water to precipitate crystals which were collected by filtration. The crystals were dissolved in chloroform and washed with 0.5 M sodium hydrogencarbonate solution and then with water. The chloroform solution was dried on anhydrous sodium sulfate. Evaporation of the solvent and recrystalization from an appropriate solvent gave a pure product. The results are summarized in Table 2.

*Reaction of α-Chloro-α,α-diphenyl-*N*-phenylacetimidoyl Chloride (6a) in the Presence of Sulfuric Acid.* 15 ml of concd H_2SO_4 was slowly added dropwise to a solution of 1.5 g of **6a** in 15 ml of acetic acid and then heated at 60 °C for 30 min. The reaction mixture was poured into 60 ml of water to give precipitates, which were treated as mentioned in the last section. 1.2 g (96%) of 3,3-diphenyloxindole (**8a**) was obtained.

Reaction of N*-Benzylbenzilamide (7b) in the Presence of Sulfuric Acid.* 15 ml of concd H_2SO_4 was added dropwise to a solution of 1.6 g of **7b** in 15 ml of acetic acid. The product was treated similarly as above, 1.2 g (80%) of 4,4-diphenyl-1,2,3,4-tetrahydroisoquinoline-3-one (**8b**) being obtained.

*Hydrolysis of 2,2-Dichloro-3-methyl-3-phenyl-1-(*m*-tolyl)aziridine (2).* A solution of 3 g of **2** in 15 ml of dioxane and 5 ml of water was refluxed for 2 h. Evaporation and recrystalization from ethanol gave 1.5 g (62%) of *N*-(*m*-tolyl)-atropamide.

Hydrolysis of 2,2-Dichloro-1-phenethyl-3,3-diphenylaziridine (3c). A solution of 3 g of **3c** in a mixture of dioxane and 5 ml of water was refluxed for 2 h. After evaporation and recrystallization from ethanol, 2 g (74%) of *N*-phenethylbenzilamide was obtained; mp 144—145 °C (lit. 139 °C); IR (KBr) 3225 cm^{-1} (NH), 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ (ppm) 7.3 (m, 15, aromatic), 3.93 (s, 1, OH), 3.60 (t, 2, $NH-\underline{CH_2}-CH_2-$), 2.80 (t, 2, $NH-CH_2-\underline{CH_2}-$); found: C, 80.12; H, 6.39; N, 4.26%, calcd for $C_{22}H_{21}NO_2$: C, 79.76; H, 6.34; N, 4.23%.

Pyrolysis of 2,2-Dichloro-1,3,3-triphenylaziridine (3a). A solution of 3.4 g of **3a** in *p*-xylene was refluxed for 1 h. Evaporation and recrystalization from hexane gave 2.4 g (70.6%) of α-chloro-α,α-diphenylacetimidoylchloride (**6a**); mp 68—69 °C (lit, 70—71 °C)2); IR (KBr); 1680 cm^{-1} (C=N); found: C, 70.54; H, 4.40; N, 3.94, calcd for $C_{20}H_{15}NCl_2$: C, 70.59; H, 4.41; N, 4.12%.

References

1) E. K. Fields and J. M. Sandri, *Chem. Ind.* (*London*), **1959**, 1216.

2) K. Ichimura and M. Ohta, *Bull. Chem. Soc. Jpn.*, **40**, 1933 (1967).

3) R. E. Brooks, J. O. Edwards, G. Levey, and F. Smyth, *Tetrahedron*, **22**, 1279 (1966).

4) P. K. Kadaba and J. O. Edwards, *J. Org. Chem.*, **25**, 1431 (1960).

5) J. A. Derup and R. B. Greenwald, *Tetrahedron Lett.*, **1965**, 321.

6) A. G. Cook and E. K. Fields, *J. Org. Chem.*, **27**, 3686 (1962).

7) D. Klamann, H, Wache, K. Ulm, and F. Nerdel, *Chem. Ber.*, **100**, 1870 (1967).
8) M. K. Meilahn, L. L. Augenstein, and J. L. McManaman, *J. Org. Chem.*, **36**, 3627 (1971).
9) L. Ross and C. Barclay, "Friedel-Crafts and Related Reaction," Vol. 2, Part 2, ed. by G. A.Olah, Interscience Publischers, New York (1964), p. 847.
10) P. A. Petyunin and I. S. Berdinsky, *J. Gen Chem. U. S. S. R.*, **21**, 1877 (1951).
11) P. A. Petyunin, *J. Gen Chem. U. S. S. R.*, **22**, 761 (1952).