Oxidation of Cyclopropylamines and Aziridines with Lead Tetraacetate

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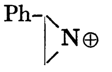
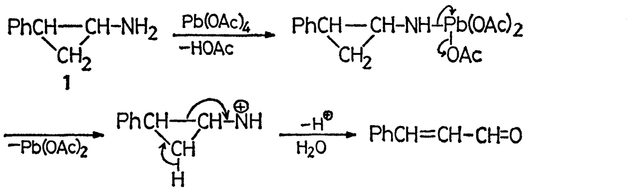
The title reaction of 2-phenylcyclopropylamine gives cinnamaldehyde, while that of the 1-phenyl isomer produces benzonitrile and ethylene. The similar treatment of 2-phenylaziridine provides benzaldehyde as the only isolable product. These reactions are explained by assuming the common intermediacy of nitrenium ions such as  and  respectively. The assumption is confirmed by the oxidation of the corresponding amines with sodium hypochlorite. Entention of the reaction to 2,3-polymethyleneaziridines with R group on C-2 afforded R–CO–$(CH_2)_n$–C≡N type products (R=H, alkyl, phenyl) in preparative yields. This provides a novel method of C=C bond cleavage of cycloalkenes.

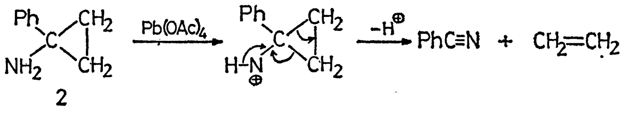
Information on reactive metastable species has been accumulating.1) Among them much attention has been focused on the oxidation of amines with metal salts in higher valency.2) The species involved in the oxidation are nitrenium ions, nitrogen radicals,3) and nitrenes.4) We wish to report that the lead tetraacetate oxidation of cyclopropylamines and aziridines proceeds *via* nitrenium ion intermediates.5)

The *trans* isomer of 2-phenylcyclopropylamine (**1**) in dichloromethane was treated with equimolar lead tetraacetate at −78 °C to afford *trans*-cinnamaldhyde. The oxidation of the *cis* isomer of **1** gave the same product. The regioisomer, 1-phenylcyclopropylamine (**2**), reacted in a completely different way to produce benzonitrile and ethylene, the latter being ascertained by obtaining 1,2-dibromoethane.

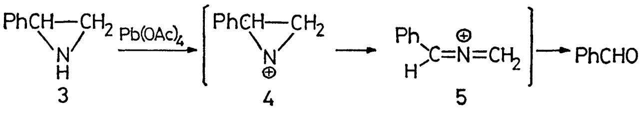
Nitrene intermediates in these reactions are excluded on the basis of the following facts. Thermal decomposition of cyclopropyl azides results in the ring expansion to yield 1-azetines.6) This transformation involves cyclopropylnitrene intermediates.6c) In contrast, however, fragmentation to olefins and nitriles is observed when appropriately substituted cyclopropyl azides are decomposed.7) The choice of either ring expansion or fragmentation seems to depend upon the substituents on the cyclopropane ring. The fragmentation is particularly favored in the one that partial positive charge being developed in the transition state resides on the remaining nitrogen upon the extrusion of nitrogen molecule.7)

More appropriately the above oxidation can be explained by assuming the intermediacy of nitrenium ions.8) In order to confirm this, the amines *trans*-**1** and **2** were treated successively with sodium hypochlorite and with silver perchlorate. The products obtained under such nitrenium ion producing conditions9) were the same as in the above oxidation, *i.e.*, cinnamaldehyde from *trans*-**1** and benzonitrile from **2**.

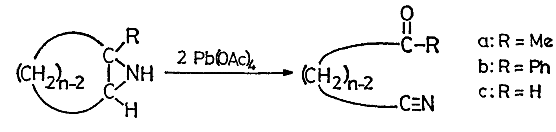




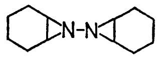
Oxidation of 2-phenylaziridine (**3**) gave benzaldehyde as a sole isolable product. Possibly the reaction involves nitrenium ion intermediate **4**10) and the 2-azaallene cation **5**,11) which is then oxygenated to benzaldehyde. With this observation in hand we examined lead tetraacetate oxidation of aziridines fused with medium and large rings.



The aziridine **6a** dissolved in dichloromethane was treated with lead tetraacetate under a nitrogen atmosphere at −40 °C. Stirring for 1 hr at −40 °C, warming up to room temperature during 2 hr and work-up gave 12-cyano-2-dodecanone (**7a**). Best results were obtained upon the use of two molar equivalent of lead tetraacetate. The structure of the product was unambiguously confirmed by the alternative synthesis of **7a**. Namely, ethyl acetoacetate was alkylated with 1,9-dibromononane and the resulting product was heated in aqueous dimethyl sulfoxide containing sodium cyanide. Both decarboxylation12) and substitution of cyano group for bromine were attained in this single operation yielding **7a**. The oxidation was extended to aziridines **6b**, **6c**, **8a**—**c**, and to the nonamethylene homologue **11a**. The yields as well as the physical properties of the products are listed in



6(n=12) 8(n=8) 7(n=12) 9(n=8)
10(n=6) 11(n=11) 12(n=11)

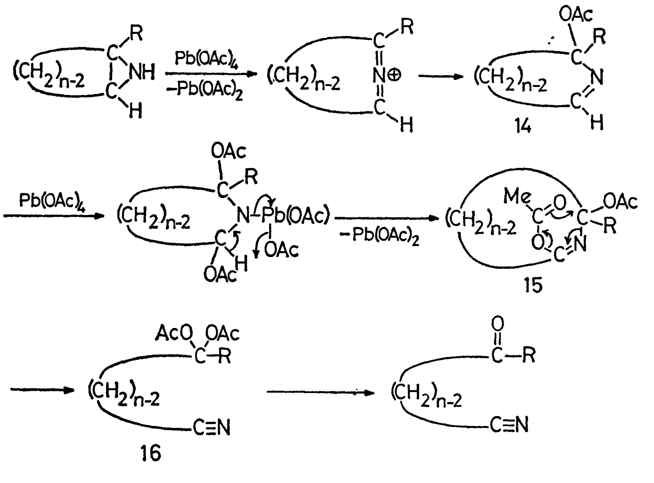


13

Table 2. In contrast to the above results, 7-azanorcarane (**10c**) was recovered unchanged under the typical condition, but the reaction at reflux of dichloromethane gave a product tentatively assigned as 7,7′-bi-7-azanorcarane (**13**).

The mechanism of the novel transformation can be understood by the following scheme involving two moles of lead tetraacetate. A cyclic 2-azaallene cation is readily susceptible to nucleophilic attack of acetate anion to give **14**. Addition of lead tetraacetate on the C=N bond in **14** followed by elimination yields **15**. Facile thermal rearrangement affords a *gem*-diacetate **16**, characterized by the spectrometry of the crude product (1735—1744 cm^{-1}, $\delta \sim 2.0$ (singlet)). Purification upon silica gel tlc induces the hydrolysis of **16** to give the corresponding ω-cyano carbonyl compound. Obviously **10c** should give a nitrenium ion which can not be isomerized to a seven-membered azaallene cation due to the strain. This accounts for the formation of **13**.

The transformation of an olefin into an ω-cyanoaldehyde has been previously achieved by the addition of nitrosyl chloride and the following Beckmann rearrangement.[13] The present method is more generally applicable, as the 2-substituted aziridines are easily obtained from cyclic ketone oximes by means of the Neber reaction[14] proceeding in the presence of Grignard reagents or organolithiums.



Experimental

IR spectra were recorded on a Shimadzu IR-27 G spectrometer, mass spectra on a Hitachi RMU-6L machine, and PMR spectra on a Varian EM 360 spectrometer (60 MHz) in carbon tetrachloride solution. All the temperatures recorded are uncorrected.

*Oxidation of Amines **1**, **2**, and **3** with Lead Tetraacetate. A General Procedure.* To a solution of lead tetraacetate (490 mg, 1.1 mmol) in dichloromethane (20 ml) an amine (1.0 mmol) dissolved in dichloromethane (5 ml) was added dropwise under a nitrogen atmosphere at −78 °C. The mixture was then gradually warmed up to room temperature in *ca.* 10 hr. Isolation of the product was accomplished by concentration of the reaction mixture, followed by preparative tlc. The product was identified by the comparison of its spectral data with those of the authentic specimen. The results are summarized in Table 1. The yields were estimated either by the isolation or glc assay as indicated.

Table 1. Oxidation of **1**, **2**, and **3**

Amine	Oxidant	Product	Yield (%)
trans-**1**	$Pb(OAc)_4$	PhCH=CHCHO	79[a]
trans-**1**	NaOCl	PhCH=CHCHO	34[a]
cis-**1**	$Pb(OAc)_4$	PhCH=CHCHO	84[a]
2	$Pb(OAc)_4$	PhC≡N[c]	69[b]
2	NaOCl	PhC≡N	21[b]
3	$Pb(OAc)_4$	PhCHO	42[b]

a) Isolation yield. b) Estimated by gas chromatographic assay. c) The accompanying ethylene was identified as 1,2-dibromoethane.

Oxidation of Amines trans-*1 and 2 with Sodium Hydrochlorite.* An amine (0.6 mmol) was added to ice-cooled commercially available aqueous sodium hypochlorite (5% content, 5.2 g) at 0 °C. The mixture was stirred at 0 °C for 10 min and then at room temperature for 1 hr. Extractive work-up with ether gave a crude product which was treated with silver perchlorate (166 mg) in acetone (5 ml) for a night. The results are listed in Table 1.

Oxidation of 2,3-Polymethyleneaziridines. A Typical Procedure: Aziridine **6a** (197 mg, 1.0 mmol) dissolved in dichloromethane (4 ml) was added to a solution of lead tetraacetate (1.00 g, 2.3 mmol) in dichloromethane (15 ml) under a nitrogen atmosphere at −40 °C. Precipitation of lead diacetate immediately occurred. The mixture was gradually warmed up to room temperature in 6 hr and then concentrated *in vacuo*. The product **7a** (171 mg, 82% yield) was separated from lead diacetate by preparative tlc on silica gel (*n*-hexane/ether 3 : 1, R_f 0.4). The yields and the physical properties of the products are collected in Table 2.

*1-Methyl-13-azabicyclo[10.1.0]tridecane (**6a**).* A methylmagnesium iodide solution prepared from methyl iodide (11.4 g, 80 mmol) and magnesium (2.0 g, 82 mmol) in ether (20 ml) was diluted with toluene (20 ml) and then cyclododecanone oxime (3.94 g, 20 mmol) was added. Ether was removed by heating the mixture and the remaining toluene solution was heated to reflux overnight. The mixture was poured into ice-cooled aqueous ammonium chloride and extracted with benzene. Work-up and distillation at 89—90 °C/0.1 mmHg gave the aziridine **6a** (2.19 g, 56% yield), mp 33.0—33.5 °C (*n*-hexane). IR (neat): 3250, 888 cm^{-1}, PMR: δ 0.9—2.4 (m+s (δ 1.17), methylenes, methyl and methine), mass: *m/e* 195 (M^+), 194 (M^+-1), 180 (M^+-15). Found: C, 79.8; H, 13.2; N, 7.4%. Calcd for $C_{13}H_{25}N$: C, 79.9; H, 12.9; N, 7.2%

*1-Phenyl-13-azabicyclo[10.1.0]tridecane (**6b**).* Cyclododecanone oxime (5.91 g, 30 mmol) and toluene (70 ml) were added to an ethereal solution of phenyllithium (prepared from lithium dispersion (1.75 g) in ether (50 ml) and bromobenzene (18.8 g, 120 mmol)). The resulting suspension was concentrated to remove ether and heating was continued for 24 hr (bath temperature 140 °C). Work-up and column chromatography (silica gel, *n*-hexane/ether 1 : 1) afforded **6b** (6.19 g, 80%), mp 55—56 °C (*n*-hexane). IR (Nujol): 3230, 1604, 1580, 763, 701 cm^{-1}, PMR: δ 0.5 (br s, 1H, NH), 0.8—2.2 (m, 21H, methylenes and methine), 7.10 (s, 5H, Ph). Mass: *m/e* 257 (M^+), 256 (M^+-1), 148 (100%). Found: C, 83.8; H, 10.8; N, 5.7%. Calcd for $C_{18}H_{27}N$: C, 84.0; H, 10.6; N, 5.4%.

*13-Azabicyclo[10.1.0]tridecane (**6c**).* A mixture (*ca.* 1 : 1) of *cis*- and *trans*-cyclododecene (1.66 g, 10 mmol) was treated with silver isocyanate (2.0 g, 13 mmol) and iodine (2.54 g, 10 mmol) in tetrahydrofuran (20 ml) in a similar

TABLE 2. LEAD TETRAACETATE OXIDATION OF AZIRIDINES **6**, **8**, **10** AND **11**, AND THE PHYSICAL PROPERTIES OF THE PRODUCTS

Aziridine	Product	Yield (%)	Bp or Mp	IR (cm^{-1})[a]	NMR (δ)
6a	**7a**[b]	82	110 °C/0.09 mmHg (bath temp)	2260, 1713	0.9—2.0 (m, 16H, methylenes), 1.98 (s, 3H, Me), 2.1—2.5 (m, 4H, CH_2CO and CH_2CN)
6b	**7b**[c]	85	54—550C (*n*-hexane)	2270, 1678[d] 1600, 1580	1.0—2.0 (m, 16H, methylenes), 2.27 (t, J=6 Hz, 2H, CH_2CN), 2.90 (t, J=6 Hz, 2H, CH_2CO), 7.2—7.7 (m, 3H, Ph-*m,p*), 7.8—8.1 (m, 2H, Ph-*o*)
6c	**7c**[e]	58	2,4-DNPH[f] 91—92 °C	2725, 2250 1723	1.0—2.0 (m, 16H, methylenes), 2.0—2.6 (m, 4H, CH_2CO and CH_2CN), 9.77 (t, J=1.8 Hz, 1H, CHO)
8a	**9a**[g]	58	120 °C/2.5 mmHg	2260, 1711	1.0—2.0 (m, 8H, methylenes), 2.06 (s, 3H, Me), 2.2—2.6 (m, 4H, CH_2CO and CH_2CN)
8b	**9b**[h]	46	41—41.5 °C (*n*-hexane)	2255, 1677[d] 1600, 1580 742, 727, 690	0.8—2.0 (m, 8H, methylenes), 2.28 (t, J=*ca* 6 Hz, 2H, CH_2CN), 2.90 (t, J=6 Hz, 2H, CH_2CO), 7.0—7.6 (m, 3H, Ph-*m,p*), 7.8—8.1 (m, 2H, Ph-*o*)
8c	**9c**[i]	29	100 °C/0.07 mmHg 2,4-DNPH[j] 75—77 °C	2730, 2255 1722	1.0—2.0 (m, 8H, methylenes), 2.0—2.8 (m, 4H, CH_2CO and CH_2CN), 11.07 (t, J=1.4 Hz, 1H, CHO)
11a	**12a**[k]	82	140—145 °C/6 mmHg (bath temp)	2260, 1716	0.6—2.0 (m, 14H, methylenes), 2.09 (s, 3H, Me), 2.1—2.6 (m, 4H, CH_2CN and CH_2CO)
10c	**13**[l]	—		955, 840, 790	0.8—2.0 (m)

a) Neat unless otherwise stated. b) Mass: *m/e* 209 (M$^+$). Found: C, 74.6; H, 11.1; N, 6.7%. Calcd for $C_{13}H_{23}NO$: C, 74.6; H, 11.1; N, 6.7%. c) Mass: *m/e* 291 (M$^+$). Found: C, 79.9; H, 9.3; N, 5.2%. Calcd for $C_{18}H_{25}NO$: C,79.7; H, 9.3; N, 5.2%. d) Nujol. e) Mass: *m/e* 195 (M$^+$). f) Lit., 90—92 °C (Ref. 13). g) Mass: *m/e* 153 (M$^+$). Found: C, 70.4; H, 10.0; N, 9.2%. Calcd for $C_9H_{15}NO$: C, 70.6; H, 9.9; N, 9.1%. h) Mass: *m/e* 215 (M$^+$). Found: C, 78.1; H, 8.2; N, 6.4%. Calcd for $C_{14}H_{17}NO$: C, 78.1; H, 8.0; N, 6.5%. i) Mass: *m/e* 139 (M$^+$). j) Lit., 76—77 °C (Ref. 13). k) Mass: *m/e* 195 (M$^+$). Found: C, 73.6; H, 11.1; N, 7.2%. Calcd for $C_{12}H_{21}NO$: C, 73.8; H, 10.8; N, 7.2%. l) Mass: *m/e* 192 (M$^+$).

manner as the reported procedure[15] to obtain methyl 2-iodocyclododecanecarbamate, mp 108—109.5 °C (*n*-hexane), IR (Nujol): 3200, 1692, 1536 cm^{-1}. Found: C, 45.9; H, 7.2; N, 3.7%. Calcd for $C_{14}H_{26}INO_2$: C, 45.8; H, 7.1; N, 3.8%.

The carbamate (1.11 g, 30 mmol) was heated in methanol (40 ml) and water (8ml) containing sodium hydroxide (2.4 g, 60 mmol) for 2 hr. Work-up followed by distillation at 120—130 °C (bath temperature)/0.2 mmHg gave the aziridine **6c** (490 mg, 90% yield), mp 46.5—47.5 °C (*n*-hexane), IR (neat): 3250, 969, 874 cm^{-1}. Found: C, 79.4; H, 12.9; N, 7.8%. Calcd for $C_{12}H_{23}N$: C, 79.5; H, 12.8; N, 7.7%.

1-Methyl-9-azabicyclo[6.1.0]nonane (8a). Cyclooctanone oxime (2.82 g, 20 mmol) was treated with methylmagnesium iodide (*ca.* 80 mmol) in toluene (10ml) and ether (25 ml) in a similar manner as **6a** to give **8a** (1. 92 g, 51% yield), bp 54 °C/4 mmHg. IR (neat): 3250, 830 cm^{-1}, PMR: δ 1.0—2.4 (m+s (δ 1.15)), mass: *m/e* 139 (M$^+$), 138 (M$^+$ −1). Found: C, 77.3; H, 12.5; N, 9.8%. Calcd for $C_9H_{17}N$: C, 77.6; H, 12.3; N, 10.1%.

1-Phenyl-9-azabicyclo[6.1.0]nonane (8b). The aziridine was obtained in 62% yield, bp 103—105 °C/0.1 mmHg. IR (neat): 3230, 1601, 1496, 931, 809, 760, 742, 701 cm^{-1}, PMR: δ 0.7—2.7 (m, 14H), 7.0—7.7 (m, 5H), mass: *m/e* 201 (M$^+$), 200 (M$^+$−1). Found: C, 83.4; H, 9.7; N, 6.7%. Calcd for $C_{14}H_{19}N$: C, 83.5; H, 9.5; N, 7.0%.

Aziridines 8c and 10c. The aziridines were prepared according to the literature.[16]

1-Methyl-12-azabicyclo[9.1.0]dodecane (11a). The aziridine was obtained by the similar method from cycloundecanone oxime in 71% yield, bp 160—165 °C/22 mmHg. IR (neat): 3250, 894 cm^{-1}, PMR: δ 0.2—0.7 (br. s, 1H), 0.7—2.3 (m+s (δ 1.18), 22H), mass: *m/e* 181 (M$^+$). Found: C, 79.5; H, 12.8; N, 7.7%. Calcd for $C_{12}H_{23}N$: C, 79.4; H, 12.9; N, 7.6%.

Alternative Preparation of 12-Cyano-2-dodecanone (7a). Ethyl acetoacetate (1.30 g, 10 mmol) was added to sodium hydride (10 mmol) suspended in dimethoxyethane (20 ml). After the evolution of hydrogen gas ceased 1,9-dibromononane (2.86 g, 10 mmol) was added to the resulting pale yellow solution. Stirring at room temperature for two days, followed by chromatographic separation of the crude product, gave 12-bromo-3-ethoxycarbonyl-2-dodecanone (0.62 g, 54% yield based on the consumed dibromide). The alkylate was dissolved in 95% aqueous dimethyl sulfoxide (10 ml) containing sodium cyanide (9.50 g), and the solution was heated at 160—165 °C for 3 hr. Extractive work-up and the subsequent purification by preparative tlc (silica gel, ether/*n*-hexane 1 : 3, R_f 0.4—0.5) afforded **7a** (0.11 g, 28% yield). All the spectral data were identical with those of the oxidation product.

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