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The Acid-Catalyzed Ring-Opening of Cyclooctenimine Derivatives

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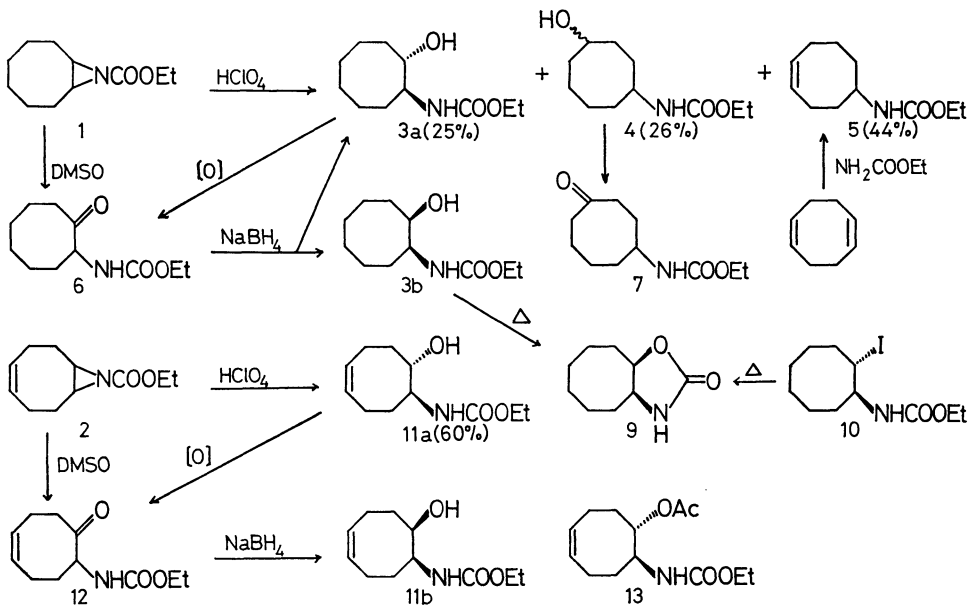
The acid-catalyzed ring-opening of 9-ethoxycarbonyl-9-aza-bicyclo[6.1.0]nonane (**1**) and -4-nonene (**2**) is reported to give normal products **3a** and **11a**, respectively, together with several transannular products.

The ring opening of cyclooctene oxide is well known,[1] and treatment of cyclooctenimine with perchloric acid results in recovery of the starting material.[2] We wish to report the acid-catalyzed aziridine ring cleavage of 9-ethoxycarbonyl-9-aza-bicyclo[6.1.0]nonane (**1**) and -4-nonene (**2**).

The reaction of **1** with perchloric acid gave ethyl *trans*-2-hydroxycyclooctane-1-carbamate (**3a**) along with two transannular products, **4** and **5**. The structure of **3a** was determined on the basis of spectral data and the following chemical correlation. Oxidation of **3a** with chromic acid gave the corresponding ketone **6** which was identical with the product prepared by the DMSO-oxidation of aziridine **1**.[3] The *trans*-configuration of **3a** was determined by hydrolysis which gave *trans*-2-aminocyclooctanol. Sodium borohydride reduction of **6** afforded **3a** as well as the *cis*-isomer (**3b**) whose configuration was established by conversion to *cis*-2-aminocyclooctanol. Heating **3b** at 170°C under reduced pressure afforded *cis*-4,5-hexamethylene-2-oxazolidone (**9**). The same compounds was obtained by thermolysis of *trans*-β-iodocarbamate (**10**). The formation of 2-oxazolidones from *N*-alkoxycarbonyl-β-aminoalcohols has not been reported.

The transannular product **4** was oxidized to the corresponding ketone (**7**) which exhibited an IR band at 1705 cm^{-1} characteristic of a medium-sized cyclic ketones. The elementary analysis and spectral data indicated that **4** was the isomer of **3a** and **3b**. The structure of **4** was tentatively assigned to be ethyl 4-hydroxycyclooctane-1-carbamate on the analogy of the formation of cyclooctane-1,4-diol in the solvolysis of cyclooctene



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2) D. V. Kashelikar and P. E. Fanta, *J. Amer. Chem. Soc.*, **82**, 4927 (1960).

3) S. Fujita, T. Hiyama and H. Nozaki, *Tetrahedron Lett.*, **1969**, 1677; *Tetrahedron*, in press.

oxide.[1] The olefinic product (**5**) was identical with the authentic ethyl 4-cyclooctene-1-carbamate prepared by the acid-catalyzed addition of urethane to 1,5-cyclooctadiene.[3]

The acid-catalyzed cleavage of **2** in aqueous phase gave ethyl *trans*-8-hydroxy-4-cyclooctene-1-carbamate (**11a**), together with a small amount of transannular by-products whose structures have not been determined. The *trans*-configuration of **11a** was established by the fact that **11a** absorbed 1 molar equivalent of hydrogen to afford **3a**. Chromic acid oxidation of **11a** yielded the corresponding ketone (**12**) which was also prepared by the DMSO-oxidation of **2**.[3] Reduction of **12** with sodium borohydride afforded ethyl *cis*-8-hydroxy-4-cyclooctene-1-carbamate (**11b**) exclusively, which on catalytic hydrogenation gave **3b**. The difference between **6** and **12** in borohydride reduction should be ascribed to the rigidity[4] of the ring of **12** as compared with that of **6**. Ethyl *trans*-8-acetoxy-4-cyclooctene-1-carbamate (**13**) was obtained by treatment of **2** with dry acetic acid along with several bicyclic minor products.

Apparently, the acid-catalyzed aziridine ring-cleavage is favored by the presence of alkoxycarbonyl group on nitrogen. Initial protonation on carbonyl oxygen[5] would account for this rather unusual activation. Formation of the transannular products may be explained by intramolecular hydride shift analogous to the solvolysis of cyclooctene oxide.[1]

The normal addition products **3a** and **11a** have *trans* configuration, where the so-called "borderline" S_N2 mechanism should be involved in a stereochemical sence.[6]

Experimental

Acid-catalyzed Hydrolysis of 1. A solution of aziridine (**1**)[3] (1.27 g, 65 mmol) in ether (12 m*l*) was added dropwise for 5 min at room temperature to a mixture of water (0.80 g), ether (15 m*l*) and 60% perchloric acid (0.30 g). After being stirred for 6.5 hr, the reaction mixture was neutralized with aqueous sodium bicarbonate, extracted with ether and dried over sodium sulfate. Concentration and separation through a Silica gel column (benzene - ether (4 : 1) as a solvent) afforded ethyl 4-cyclooctene-1-carbamate (**5**) (0.56 g, 44%), which was identical with the authentic sample.[3]

Subsequent elution with ether gave ethyl *trans*-2-hydroxycyclooctane-1-carbamate (**3a**) (0.35 g, 25%), bp 140—145°C/0.05 mmHg, mp 42—43°C (*n*-hexane - acetone). IR (neat): 3450—3300 (broad), 1690, 1535, 1300, 1250—1235, 1090, 1035 cm^{-1}. NMR (CCl_4): δ 5.7—5.3 (broad, 1H, NH), 4.09 (q, 2H, $OC\underline{H}_2CH_3$), 4.0—3.3 (m, 3H, methines and OH), 2.4—1.0 (m, 12H, methylenes), 1.28 (t, 3H, $OCH_2C\underline{H}_3$).

Found: C, 61.4; H, 10.0; N, 6.8%. Calcd for $C_{11}H_{21}NO_3$: C, 61.4; H, 9.8; N, 6.5%.

The third eluent was ethyl 4-hydroxycyclooctane-1-carbamate (**4**) (0.36 g, 26%) bp 150—155°C/0.05 mm Hg IR (neat): 3450—3330 (broad), 1685, 1530, 1300, 1235, 1090, 1059, 1028 cm^{-1}. NMR (CCl_4): 6.0—5.3 (broad, 1H, NH), 4.3—3.4 (m+q, 5H, methines, OH and $OC\underline{H}_2CH_3$), 2.5—1.3 (m, 12H, methylenes), 1.25 (t, 3H, $OCH_2C\underline{H}_3$).

Found: C, 61.4; H, 10.0; N, 6.5%. Calcd for $C_{11}H_{21}NO_3$: C, 61.4; H, 9.8; N, 6.5%.

Oxidation of 4. (0.12 g, 0.56 mmol) by the Brown procedure[7] and subsequent preparative thin-layer chromatography (TLC) afforded ethyl 4-cyclooctanone-1-carbamate (**7**), bp 110—115°C/0.5 mm. IR (neat): 3350, 1705, 1675, 1530, 1380, 1340, 1225, 1040 cm^{-1}. NMR (CCl_4): δ 4.87 (s, 1H, NH), 4.14 (q, 2H, $OC\underline{H}_2CH_3$), 3.9—3.4 (m, 1H, methine), 2.7—1.0 (t+m, 15H, $OCH_2C\underline{H}_3$ (δ 1.30) and methylenes).

Found: C, 62.5; H, 9.1; N, 6.6%. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6%.

Oxidation of 3a. (0.12 g, 0.56 mmol) by the Brown procedure[7] gave ethyl 2-oxocyclooctane-1-carbamate (**6**), whose IR and NMR spectra were identical with those of the sample prepared by the DMSO-oxidation of **1**.[3]

Reduction of 6 with Sodium Borohydride. Sodium borohydride (0.10 g) was added in one portion to a solution of **6** (0.15 g, 0.70 mmol) in methanol at 0°C. After being stirred for 4 hr, and suspension was acidified to pH 4 by dilute hydrochloric acid, poured into water, extracted with ether and dried. Concentration and separation by preparative TLC afforded **3a** (0.025 g, 17%) as well as ethyl *cis*-2-hydroxycyclooctane-1-carbamate (**3b**) (0.040 g, 26%), bp 160°C/1 mmHg. IR (neat): 3450—3350 (broad), 1685, 1520—1510, 1310, 1248, 1107, 1090, 1060, 1035 cm^{-1}. NMR (CCl_4): δ 5.7—5.2 (broad, 1H, NH), 4.2—3.5 (m+q, 4H, methines and $OC\underline{H}_2CH_3$), 3.4—3.0 (broad, 1H, OH) 2.0—1.0 (m+t, 13H, methylenes and $OCH_2C\underline{H}_3$) (δ 1.20)).

Found: C, 61.3; H, 9.9; N, 6.2%. Calcd for $C_{11}H_{21}NO_3$: C, 61.4; H, 9.8; N, 6.5%.

Hydrolysis of 3a. A mixture of **3a** (0.26 g, 1.2 mmol), sodium hydroxide (1.5 g), methanol (10 m*l*) and water (10 m*l*) was refluxed under nitrogen atmosphere for 25 hr. Usual work-up gave *trans*-2-aminocyclooctanol (0.18 g) quantitatively, mp 72.6—73°C (lit,[8] mp 73—74°C).

Hydrolysis of 3b. (0.050 g, 0.23 mmol) with methanolic sodium hydroxide yielded *cis*-2-aminocyclooctanol (0.030 g, 90%) as a solid, whose IR spectrum was identical with that of the sample prepared from the oxazolidone (**9**).

***cis*-4,5-Hexamethylene-2-oxazolidone (9).** A solution of β-iodocarbamate **10**[3] (5.0 g, 15 mmol) in xylene (40 m*l*) was heated for 20 hr. Concentration and recrystallization gave the oxazolidone (**9**) (2.57 g) quantitatively, mp 106.5—107.5°C (acetone). IR (Nujol): 3260, 3170, 1745, 1725, 1260, 1235, 1090, 1080, 1042,

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974 cm^{-1}. NMR (CCl_4): δ 7.4—7.1 (broad, 1H, NH), 4.8—4.2 (m, 1H, CH–O), 4.1—3.5 (m, 1H, CH–N), 2.4—1.0 (m, 12H, methylenes).

Found: C, 63.7; H, 9.1; N, 8.2%. Calcd for $C_9H_{15}NO_2$: C, 63.9; H, 8.9; N, 8.3%.

The same oxazolidone (**9**) was obtained by distillation of **3b** at 170°C/1.5 mmHg.

Hydrolysis of 9. (1.69 g, 10 mmol) with alcoholic potash afforded *cis*-2-aminocyclooctanol (1.40 g, 98%), mp 45—47°C (*n*-hexane - benzene) (lit,[8] mp 52—54°C).

Acid-catalyzed Hydrolysis of 2. Aziridine **2**[3] (4.68 g, 24 mmol) was treated with perchloric acid as described above. Recrystallization of the crude solid (5.6 g) gave ethyl *trans*-8-hydroxycyclooct-5-ene-1-carbamate (**11a**) (2.38 g), mp 98.8—99.5°C (ethyl acetate – *n*-hexane). IR (Nujol): 3420, 3290, 3090, 3040, 1690, 1550, 1260, 1329, 1154, 1130, 1060, 1042 cm^{-1}. NMR ($CDCl_3$): δ 5.8—5.5 (m, 2H, olefinic), 5.4—5.0 (broad, 1H, NH), 4.3—3.5 (m+q, 4H, methines and $OC\underline{H}_2CH_3$), 2.80 (s, 1H, OH), 2.7—1.3 (m, 8H, methylenes), 1.26 (t, 3H, $OCH_2C\underline{H}_3$).

Found: C, 61.7; H, 9.0; N, 6.5%. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6%.

The mother liquor was submitted to chromatography on Silica gel. Elution with benzene - ether (3 : 1) gave an isomerization product (0.68 g, 15%), bp 100—110°C/0.04 mmHg. IR (neat): 3320, 1690, 1525, 1230, 1080, 1045 cm^{-1}. NMR (CCl_4): δ 5.9—5.2 (m, 4H, olefinic and NH), 4.07 (q, 2H, $OC\underline{H}_2CH_3$), 2.7—1.3 (m, 8H, methylenes), 1.23 (5, 3H, $OCH_2C\underline{H}_3$). MS *m/e* 195 (M^+). The compound was tentatively assigned as ethyl 1,5-cyclooctadiene-1-carbamate.

Found: C, 67.4; H, 8.8; N, 7.0%. Calcd for $C_{11}H_{17}NO_3$: C, 67.7; H, 8.8; N, 7.2%.

Further elution with benzene - ether (1 : 1) gave additional **11a** (0.70 g, totally 3.08 g, 60%). The third component was an oil (0.24 g, 5%), bp 120—130°C/0.05 mmHg. IR (neat): 3450—3330, 1688, 1535, 1288, 1240, 1098, 1070, 1046 cm^{-1}. NMR (CCl_4): δ 5.7—5.4 (broad, 1H, NH), 4.9—4.5 (m, 1H, methine), 4.3—3.5 (m+q, methine and $OC\underline{H}_2CH_3$), 2.93 (s, 1H, OH), 2.6—0.8 (m+t, 13H, methylenes and $OCH_2C\underline{H}_3$). MS *m/e* 213 (M^+). The compound was tentatively assigned as ethyl 6-hydroxybicyclo [3.3.0] octane-2-carbamate, since the corresponding ketone obtained by its oxidation exhibited an IR band at 1735 cm^{-1} characteristic of a five-membered cyclic ketone.

Oxidation of 11a (0.43 g, 2.0 mmol) with chromic acid[7] gave an oil (0.37 g, 88%), which was identical with the sample of **12** prepared by the DMSO-oxidation of **2**.

Sodium Borohydride Reduction of 12 (0.75 g, 3.5 mmol) and subsequent chromatography on Silica gel column gave ethyl *cis*-8-hydroxy-4-cyclooctene-1-carbamate (**11b**) (0.63 g, 83%), mp 93.5—94.5°C (acetone). IR (Nujol): 3420, 3280, 1690, 1550, 1255, 1235, 1060, 1040 cm^{-1}. NMR ($CDCl_3$): δ 5.8—5.4 (m, 3H, olefinic and NH), 4.3—3.6 (m+q, 5H, OH, methines and $OC\underline{H}_2CH_3$), 2.9—1.5 (m, 8H, methylenes), 1.26 (t, 3H, $OCH_2C\underline{H}_3$).

Found: C, 61.8; H, 9.1; N, 6.4%. Calcd for $C_{11}H_{19}NO_3$: C, 61.9; H, 9.0; N, 6.6%.

Hydrogenation of 11a. A mixture of **11a** (0.50, 2.4 mmol), Raney's nickel (*ca.* 0.3 g) and ethanol (10 m*l*) was stirred under hydrogen atmosphere at room temperature until 1 molar hydrogen was absorbed (*ca.* 24 hr). The catalyst was filtered, washed exclusively with ether and the combined washings were evaporated *in vacuo*, yielding **3a** as an oil (0.51 g, quantitatively).

Hydrogenation of 11b. (0.26 g, 1.2 mol) gave **3b** (0.23 g, 90%) as a colorless oil, which was identical with the sample obtained by reduction of **6**.

Solvolysis of 2 in Acetic Acid. A solution of **2** (1.56 g, 8 mmol) in glacial acetic acid (5 m*l*) was added dropwise under nitrogen atmosphere to a mixture of acetic acid (8 m*l*), acetic anhydride (3 drops) and BF_3-etherate (10 drops) at 50—55°C. After stirring for 3 hr and usual work-up, chromatography on Silica gel gave the isomerization product (0.22 g, 14%) which was identical with the one obtained by the hydrolysis of **2**. The second eluent was ethyl *trans*-8-acetoxy-4-cyclooctene-1-carbamate (**13**) (0.92 g, 45%), bp 110—120°C/0.05 mmHg. IR (neat): 3350, 1724, 1700, 1530—1510, 1230, 1050, 1032 cm^{-1}. NMR (CCl_4): δ 5.8—5.5 (m, 2H, olefinic), 5.1—4.5 (m, 2H, methine and NH), 4.3—3.7 (m+q, 3H, methine and $OC\underline{H}_2CH_3$), 2.5—1.4 (m+s, 11H, methylenes and AcO (δ 2.00)), 1.22 (t, 3H, $OCH_2C\underline{H}_3$).

Found: C, 60.9; H, 8.3; N, 5.5%. Calcd for $C_{13}H_{21}NO_4$: C, 61.2; H, 8.3; N, 5.5%.

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