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Syntheses and the Beckmann Fission of Cyclic α-Hydroxyimino Ketones

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A convenient method for the preparation of α-hydroxyimino cycloalkanones has been established by the reaction of cycloalkanones and nitrosyl chloride. ω-Cyanocarboxylic acids or their derivatives were obtained in good yield by the Beckmann rearrangement of these α-hydroxyimino ketones.

Nitrosyl chloride addition to cycloolefins followed by displacement reactions with nucleophilic reagents such as alcohols, thioalcohols, and alkylamines provides a method of preparing various α-substituted oximes[1] which are attractive intermediates for the Beckmann fission.[2] The overall sequence is equivalent to a cleavage of the double bond in the cycloolefins, affording ω-cyanoaldehydes.[3]

No attempt has been made to prepare ω-cyanocarboxylic acids expected from the cleavage of cyclic α-hydroxyimino ketones,[4,5] from cycloalkanones such as cyclohexanone, cyclooctanone, and cyclododecanone.

In the present paper, we wish to report a convenient method for preparing α-hydroxyimino ketones of medium rings from ketones and the Beckmamm fission of such α-hydroxyimino ketones into ω-cyanocarboxylic acids. The results are compared with those of six-membered ring system.

Results and Discussion

Preparation of Cyclic α-Hydroxyimino Ketones. Although the preparation of acyclic α-hydroxyimino ketones from acyclic ketones or β-keto acids is well-known,[6] there is little information on the synthetic application of cyclic α-hydroxyimino ketones. We became interested in the study of α-hydroxyimino ketones of medium ring system, since these cyclic parent compounds are now easily available.[7]

Cyclododecanone and cyclooctanone were treated with an equivalent amount of nitrosyl chloride in the presence of a catalytic amount of hydrogen chloride, affording 2-hydroxyiminocyclododecanone (I) and 2-hydroxyiminocyclooctanone (II) in quantitative and in 87% yields, respectively. It was found that the presence of hydrogen chloride was essential at the beginning of the reaction, no reaction taking place or a long induction peiord being observed in its absence. The action of hydrogen chloride must be the enolization of the ketones as seen in typical cases of nitrosating agents such as alkyl nitrite–alkoxide and alkyl nitrite–hydrogen chloride.[6] I was obtained in the state of hydrochloride, being deposited during nitrosation from the reaction medium such as ether or petroleum benzine at low temperatures (0—5 °C), and the hydrochloride was easily transformed into the free oxime simply by being warmed up to room temperature. However, it was necessary to neutralize the hydrochloride of II with sodium bicarbonate to transform it into the free form. Neither dinitrosation nor nitrosochlorination was observed in the reactions of cyclododecanone and cyclooctanone.

Nitrosation of cyclohexanone was studied in detail by several groups, and it was found that dinitrosation occurs very easily. Ferris prepared 2,6-dihydroxyiminocyclohexanone by the reaction of cyclohexanone and methyl nitrite as a key intermediate for the synthesis of lysine,[5] and Taira obtained it by treatment of

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[1] M. Ohno, N. Naruse, M. Okamoto, S. Torimitsu, and I. Sakai, This Bulletin, **39**, 1119, 1125, 1129 (1966).

[2] C. A. Grob and P. W. Shiess, *Angew. Chem.*, **79**, 1 (1967).

[3] a) M. Ohno, N. Naruse, S. Torimitsu, and I. Terasawa, *J. Amer. Chem. Soc.*, **88**, 3168 (1966). b) M. Ohno, N. Naruse, and I. Terasawa, "Organic Syntheses," Vol. 49, John Wiley & Sons, New York, N.Y. (1969), p. 27.

[4] D. Murakami and N. Tokura, This Bulletin, **31**, 1044 (1958).

[5] A. F. Ferris, G. S. Johnson, and F. E. Gould, *J. Org. Chem.*, **25**, 496 (1960).

[6] O. Touster, "Organic Reactions," Vol. 7, John Wiley & Sons, New York, N. Y. (1953), p. 327.

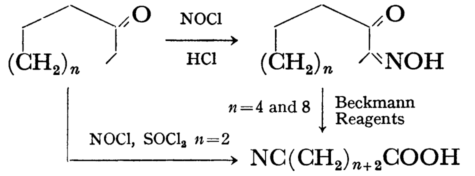
[7] G. Wilke, *Angew. Chem.*, **75**, 10 (1963).

cyclohexanone with nitrosyl chloride at temperatures above −20 °C.[8] Mononitrosation of cyclohexanone requires careful reaction conditions. Thus, 2-hydroxyiminocyclohexanone (III) was obtained by treatment with 2-ethyl-*n*-hexyl nitrite[9] or by nitrosation of 2-carbethoxycyclohexanone.[10] We found that the degree of nitrosation of cyclohexanone with nitrosyl chloride is controlled by the reaction temperature. Mononitrosation of cyclohexanone occurs below −50 °C in the presence of hydrogen chloride, and dinitrosation at temperatures above −20 °C. A mixture of mono- and dihydroxyimino compounds was obtained at temperatures −50—−20 °C. III was obtained in the state of unstable hydrochloride and free oxime was obtained in 62% yield after neutralization with aqueous sodium hydroxide.

Table 1. IR spectra of I, II, and III (in CCl_4)

α-Hydroxy-imino Ketone	mp °C	ν_{OH} (Free) cm^{-1}	ν_{OH} (Bonded) cm^{-1}	$\Delta\nu$ cm^{-1}	Configu-ration
III	60—64	3560	3240	320	*syn*
II(*syn*)	101—103	3580	3260	320	*syn*
II(*anti*)	oil	3580	—	—	*anti*
I	69—70	3560	—	—	*anti*

It should be mentioned that the configuration of the cyclic α-hydroxyimino ketones obtained depends upon the ring size. The configurations of I, II, and III were determined spectroscopically[11] and the results are shown in Table 1. The configuration of III, which so far has not been discussed, was found to be exclusively *syn*, and 8-membered α-hydroxyimino ketone (II) was shown to be a mixture of *syn* and *anti* forms in equal amount, but the configuration of I was found to be exlcusively *anti*.



Beckmann Fission of Cyclic α-Hydroxyimino Ketones. The cyclic α-hydroxyimino ketones thus obtained were subjected to the Beckmann rearrangement under various conditions. The results are summarized in Table 2. 2-Hydroxyiminocyclododecanone (I) afforded 11-cyanoundecanoic acid or its derivatives as expected from the *anti* configuration of I. However, when I was treated with phosgene, oily and crystalline substances were obtained. The former was found to be the cyanoacid chloride (VI, 39% yield) and the latter dodecanedioic imide (VIII, 6% yield). This result shows that the usual Beckmann rearrangement occurs to some extent under specific conditions. Direct treatment of cyclododecanone with nitrosyl chloride and acetic anhydride in the presence of sulfuric acid, using ether as a solvent, followed by hydrolysis, gave IV in 87% yield. This one-step Beckmann fission from the cyclic ketone seems to be specific to acetic anhydride, since the reaction did not occur when other anhydrides were used. 2-Acetoxyiminocyclododecanone (XII) prepared quantitatively by treatment of I with acetic anhydride or direct treatment of cyclododecanone with nitrosyl chloride and acetic anhydride in the presence of hydrogen chloride, underwent Beckmann fission under basic conditions using aqueous sodium hydroxide to afford IV in a quantitative yield. The results show that the choice of reagent and/or catalyst not only decides the terminal functions in various ways but also influences the mechanism of fission.

In the case of Beckmann fission of II, both forms of *syn* and *anti* configurations gave 7-cyanoheptanoic acid (XIII) in excellent yields, showing that the pattern of Beckmann rearrangement does not always depend upon the stereochemistry of the α-hydroxyimino ketone.

Treatment of 2-hydroxyiminocyclohexanone (III) which exists only in *syn* form with sulfuric acid, 97% phosphoric acid or thionyl chloride recovered most of the starting material along with some intractable tarry products, showing that the *syn* α-hydroxyimino ketone resists the Beckmann fission as expected.[12] Preparation

Table 2. Beckmann fission of α-hydroxyimino ketones

α-Hydroxyimino Ketones	Reaction Conditions	Products (Yield)
I	$97\%H_3PO_4/H_2O$	$NC(CH_2)_{10}COOH$(IV, 98%)
	H_2SO_4/H_2O	$NH_2CO(CH_2)_{10}COOH$(V,96%)
	$SOCl_2$	$NC(CH_2)_{10}COCl$ (VI, 62%)
	$SOCl_2/NH_3$	$NC(CH_2)_{10}CONH_2$ (VII, 96%)
	$COCl_2$	$(CH_2)_{10}CONHCO$ (VIII, 6%) $NC(CH_2)_{10}COCl$(VI, 39%)
	$COCl_2/MeOH$	$NC(CH_2)_{10}COOCH_3$(IX, 75%) $NH_2CO(CH_2)_{10}COOCH_3$ (X, 15%)
	Ac_2O, H_2SO_4	$NC(CH_2)_{10}COOAc$(XI, 95%)
II (*syn*)	$97\%H_3PO_4/H_2O$	$NC(CH_2)_6COOH$(XIII, 80%)
II(*anti*)	$97\%H_3PO_4/H_2O$	$NC(CH_2)_6COOH$ (XIII, 78%)

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8) S. Taira, S. Imamura, K. Yotsumoto, and K. Takada, Jap. 645957 (1972).

9) E. G. Rauh, G. F. Smith, C. V. Bank, and H. Diehl, *J. Org. Chem.*, **10**, 199 (1945).

10) F. M. Jaeger and J. A. von Dijk, *Proc. Acad. Sci. Amsterdam*, **39**, 384 (1936).

11) H. Saito, I. Terasawa, M. Ohno, and K. Nukada, *J. Amer. Chem. Soc.*, **91**, 6696 (1969).

12) A. F. Ferris, *J. Org. Chem.*, **25**, 12 (1960).

of 5-cyanovaleric acid by direct treatment of cyclohexanone with nitrosyl chloride and thionyl chloride was attempted as in the case of 12-membered ketone. Nitrosyl chloride was added to a solution of cyclohexanone and thionyl chloride in ether at −50 °C, but the fission did not occur 2-hydroxyiminocyclohexanone hydrochloride was obtained. However, when the reaction was carried out in the presence of sulfuric acid and dimethylformamide[13] as catalysts, 5-cyanovaleric acid (XIV) was successfully obtained in 60% yield. Direct methanolysis of the reaction mixture gave methyl 5-cyanovalerate (XV) in 46% yield. Thus it might be reasonable to assume that the reaction proceeds through the direct cleavage of 2-nitrosocyclohexanone or *anti* form of 2-hydroxyiminocyclohexanone before the dinitrosation of cyclohexanone or the transformation to *syn* form occurs.

Experimental

All melting points are uncorrected. The IR spectra were measured with a Hitachi EPI S-2 spectrophotometer. Hydroxyl absorption bands in the 3600 cm^{-1} region were examined in carbon tetrachloride with a Perkin-Elmer Model 125 grating spectrophotometer using 1.5 cm sodium chloride cell. The NMR spectra were measured with a Varian A 60 spectrophotometer. Molecular weights were determined with a Hitachi Perkin-Elmer Model 115 molecular weight apparatus.

2-Hydroxyiminocyclodecanone (I). Hydrogen chloride was passed through a solution of cyclododecanone (20 g) in petroleum benzine (200 ml) for 5 min with stirring at 0 °C. A solution of nitrosyl chloride (8.5 g) in the same solvent (30 ml) was then added over a period of 30 min. The mixture was stirred for 1 hr at 2 °C and the solvent was evaporated under reduced pressure. The pale yellow solid obtained was chromatographed over silica gel. The solid (21.3 g, 97%) obtained was recrystallized from petroleum ether, mp 69—70 °C.

Found: C, 68.41; H, 10.05; N, 6.70%. Calcd for $C_{12}H_{21}O_2N$: C, 68.21; H, 10.02; N, 6.63%.

When ether was employed as a solvent in the same reaction, fine crystals were deposited during the reaction. The substance was proved to be 2-nitrosocyclododecanone dimer (1%), mp 133—134 °C.

Found: C, 68.01; H, 10.00; N, 6.42%; mol wt, 431. Calcd for $C_{24}H_{40}O_4N_2$: C, 68.21; H, 10.02; N, 6.63% mol wt, 423.

2-Hydroxyiminocyclooctanone (II). Hydrogen chloride was passed through a solution of cyclooctanone (10 g) in ether (100 ml) for 3 min with stirring at −25 °C, and a solution of nitrosyl chloride (6.3 g) in the same solvent (20 ml) was added over a period of 20 min. The mixture was stirred for 10 min at −25 °C, and aqueous sodium bicarbonate was added. The organic layer was separated, washed with water and dried. The oily product obtained by evaporation of the solvent was chromatographed over silica gel. The fractions eluted first afforded the *anti* form of II as an oily substance (5.16 g, 42%); the fractions eluted next afforded the *syn* form of II as a solid product (5.54 g, 45%). The latter was recrystallized from ether, mp 101—103 °C. IR (see Table 1). Found: C, 61.97; H, 8.42; N, 8.93%. Calcd for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03%.

The oily material was further purified by silica gel chromatography; one spot on tlc. IR (see Table 1).

Found: C, 61.69; H, 8.48; N, 8.70%. Calcd for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03%.

2-Hydroxyiminocyclohexanone (III). Hydrogen chloride was saturated in a solution of cyclohexanone (10.5 g) in ether (100 ml) with stirring at −10 °C. A solution of nitrosyl chloride (4.5 g) in the same solvent (20 ml) was added over a period of 20 min at −50 °C. The mixture was stirred for 10 min at −50 °C, nitrogen was bubbled at −10 °C to remove the hydrogen chloride. Aqueous sodium hydroxide (30%) was added to the reaction mixture at −10 °C, and the pH was adjusted to 7. The ethereal layer was separated and the aqueous layer was extracted four times with chloroform. The combined organic layers were dried and the solvent was removed. The brown oil thus obtained was chromatographed over silica gel, giving III (5.52 g, 62%) as a white solid showing mp 60—64 °C. NMR (CCl_4): δ 9.2 (s, 1H), 2.79 (t, 2H), 2.47 (t, 2H), and 1.82 ppm (m, 4H).

Treatment of III with 2,4-dinitrophenylhydrazine gave the osazone, mp 216—217 °C.

Found: C, 45.96; H, 3.56; N, 23.41%; mol wt, 474. Calcd for $C_{18}H_{16}O_8N_8$: C, 45.76; H, 3.41; N, 23.72%; mol wt, 472.

11-Cyanoundecanoic Acid (IV). To a mixture of 97% phosphoric acid (10 ml) and sulfuric acid (1 ml) was added finely powdered II (1.0 g) at room temperature with stirring. The mixture was stirred for 3 hr at room temperature and poured into ice water (50 g). The mixture was extracted with ether and the extract was washed with water and dried. 11-Cyanoundecanoic acid (0.98 g, 98%) obtained after evaporation of the solvent was recrystallized from benzene–petroleum benzine, mp 54—55 °C.

Found: C, 68.34; H, 9.91; N, 6.66%. Calcd for $C_{12}H_{21}O_2N$: C, 68.21; H, 10.02; N, 6.63%.

11-Carbamoylundecanoic Acid (V). Finely powdered I (1.0 g) was added with stirring to sulfuric acid (10 ml) cooled with ice. The reaction mixture was allowed to stand at room temperature for 1.3 hr and poured into ice water (50 g). A white solid product was obtained by filtration, washed with water and dried in a vacuum desiccator. 11-Carbamoylundecanoic acid (1.04 g, 96%) obtained as white powder was recrystallized from acetone, mp 130—131 °C.

Found: C, 62.61; H, 10.14; N, 6.13%. Calcd for $C_{13}H_{23}O_3N$: C, 62.85; H, 10.11; N, 6.11%.

11-Cyanoundecanoyl Chloride (VI). A solution of thionyl chloride (6.66 g) in ether (15 ml) was added with stirring over a period of 30 min at room temperature to a solution of I (9.17 g) and dimethylformamide (1 ml) in ether (90 ml). The mixture was stirred for 30 min at room temperature and the solvent was removed under reduced pressure. The residual liquid was distilled under reduced pressure (bp 146—147 °C/2.0 Torr), affording 11-cyanoundecanoyl chloride (6.21 g, 62%) as colorless liquid.

Found: C, 62.87; H, 8.69; N, 5.92; Cl, 15.55%. Calcd for $C_{12}H_{20}ONCl$: C, 62.73; H, 8.77; N, 6.11; Cl, 15.43%.

Hydrolysis of the reaction mixture gave 11-cyanoundecanoic acid (IV) in 93% yield.

Ammonolysis of the reaction mixture gave 11-cyanoundecanoyl amide (VII) in 96% yield. It was recrystallized from benzene, mp 86—87 °C.

Found: C, 68.14; H, 10.68; N, 13.05%. Calcd for $C_{12}H_{22}ON_2$: C, 68.53; H, 10.54; N, 13.32%.

Treatment of I with Phosgene. A solution of phosgene (12 g) in dichloromethane (76 ml) was added with stirring to a solution of I (20.0 g) in the same solvent (100 ml) at room temperature. The mixture was stirred for 1.5 hr at

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[13] H. H. Bosshard, R. Mory, M. Schmid, and H. Zollinger, *Helv. Chim. Acta*, **42**, 1653 (1959).

room temperature and divided into three fractions.

(1) Water (20 ml) was added to the reaction mixture (50 ml) and the mixture was stirred for 1 hr at room temperature. The organic layer was separated and the aqueous layer was extracted with ether. Combined organic layers were washed with water and dried. Evaporation of the solvent gave a mixture of liquid and crystals. Ether (10 ml) was added to the mixture and the crystals were separated by filtration. Dodecanedioic imide (VIII, 345 mg, 6%) was obtained, recrystallized from a mixed solvent of acetone–benzene, mp 137—138 °C.

Found: C, 68.49; H, 10.05; N, 6.44%; mol wt, 214. Calcd for $C_{12}H_{21}O_2N$: C, 68.21; H, 10.02; N, 6.63%; mol wt, 211.

11-Cyanoundecanoic acid (4.08 g, 71%) and 11-carbamoylundecanoic acid (0.20 g, 3%) were separated from the liquid after being subjected to silica gel chromatography.

(2) After evaporation of the solvent of the reaction mixture (74 ml), a crystalline solid was separated by filtration. The solid was proved to be VIII. Distillation of the filtrate gave 11-cyanoundecanoyl chloride (VI, bp 134—135 °C/0.4 Torr, 3.57 g, 39%).

(3) Methanol (30 ml) was added to the reaction mixture (50 ml) and the mixture was stirred for 2 hr at room temperature. Methyl 11-cyanoundecanoate (4.6 g, 75%) and methyl 11-carbamoylundecanoate (1.0 g, 15%) were obtained after being subjected to silica gel chromatography. The former (IX) was purified by distillation, bp 133—137 °C/0.4 Torr.

Found: C, 69.19; H, 10.43; N, 6.29%. Calcd for $C_{13}H_{23}O_2N$: C, 69.29; H, 10.29; N, 6.22%.

The latter (X) was recrystallized from a mixed solvent of benzene–petroleum benzine, mp 97—98 °C.

Found: C, 64.25; H, 10.41; N, 5.75%. Calcd for $C_{13}H_{25}O_3N$: C, 64.16; H, 10.36; N, 5.76%.

Treatment of I with Acetic Anhydride and Sulfuric Acid. Three drops of sulfuric acid were added to a stirred solution of I (3.21 g) and acetic anhydride (2.0 g) in ether (35 ml), and the solution was stirred for 2 hr at room temperature. Ice water (50 g) was added to the reaction mixture and stirred for 30 min. Aqueous layer was extracted with ether and the combined organic layers were dried and the solvent was removed under reduced pressure. A mixed anhydride (XI, 3.66 g, 95%) of IV and acetic acid was obtained. IR (NaCl): 1820 and 1750 cm^{-1}. 11-Cyanoundcanoic acid (2.97 g, 93%) was obtained after being subjected to chromatography over silica gel. Ammonolysis of XI gave IV (65%) and VII (16%).

2-Acetoxyiminocyclododecanone (XII). 2-Hydroxyiminocyclododecanone (I, 2.52 g) was dissolved in acetic anhydride (10 ml) and the solution was heated at 50 °C for 1 hr. After treatment of the reaction mixture in the usual manner, acetate (XII, 2.91 g, 96%) was obtained and recrystallized from petroleum benzine, mp 60—61 °C.

Found: C, 66.46; H, 9.41; N, 5.59%. Calcd for $C_{14}H_{23}O_3N$: C, 66.37; H, 9.15; N, 5.53%.

Treatment of 2-Acetoxyiminocyclododecanone (XII) with Aqueous Sodium Hydroxide. Aqueous sodium hydroxide (5%, 20 ml) was added to a stirred solution of XII (1.5 g) in ether (2 ml), and the solution was stirred for 2 hr at room temperature. The reaction mixture was acidified with dilute hydrochloric acid and extracted with ether. 11-Cyanoundecanoic acid (1.19 g, 95%) was obtained by the usual method.

7-Cyanoheptanoic Acid (XIII). 2-Hydroxyiminocyclooctanone of *syn* form (II, *syn*) was treated with 97% phosphoric acid under the same reaction conditions as in the case of I. 7-Cyanoheptanoic acid (XIII) was obtained in 80% yield and recrystallized from petroleum ether, mp 34—35 °C. The *anti* form afforded XIII in 78% yield by the same treatment.

Found: C, 62.19; H, 8.42; N, 9.10%. Calcd for $C_8H_{13}O_2N$: C, 61.91; H, 8.44; N, 9.03%.

5-Cyanovaleric Acid (XIV) To a solution of cyclohexanone (10 g), sulfuric acid (1 ml), and dimethylformamide (5 ml) in ether (100 ml) was added a solution of nitrosyl chloride (7 g) in ether (20 ml) with stirring at −20 °C over a period of 20 min. The mixture was stirred for 10 min at −10 °C, and cooled to −30 °C. Aqueous sodium hydroxide (30%, 100 ml) was added and the mixture was stirred for 1 hr at room temperature. After separation of the ethereal layer, the aqueous layer was acidified with hydrochloric acid and extracted with dichloromethane. Evaporation of the solvent gave crude 5-cyanovaleric acid (XIV, 8.0 g) as pale brown liquid. Pure 5-cyanovaleric acid (6.8 g, 52%) was obtained by distillation under reduced pressure, bp 114—115 °C/0.2 Torr.

Found: C, 56.75; H, 7.01; N, 11.02%. Calcd for $C_6H_9O_2N$: C, 56.68; H, 7.14; N, 11.02%.

Methyl 5-cyanovalerate (XV) was obtained in 46% yield by methanolysis of the reaction mixture, bp 80—82 °C/1.0 Torr.

Found: C, 59.79; H, 7.90; N, 9.60%. Calcd for $C_7H_{11}O_2N$: C, 59.55; H, 7.85; N, 9.92%.