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BEHAVIOR OF 2-(1-CYCLOHEXENYL)CYCLOHEXANONE OXIME AND RELATED OXIMES UNDER BECKMANN REARRANGEMENT CONDITIONS

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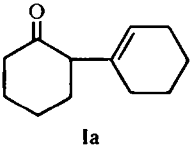
Abstract—The behavior of several alpha-monosubstituted cyclohexanone oximes under Beckmann rearrangement conditions is compared. Alpha-1-chlorocyclohexane and cyclohexane substituted oximes undergo the normal rearrangement, while the alpha-cyclohexene substitution gives rise to fragmentation products. This result is discussed. Synthesis of *6-amino-6-(1-cyclohexenyl)hexanoic acid lactam* in high yield is described.

INTRODUCTION

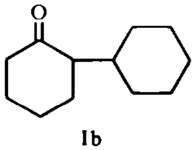
THE fission of alpha-dialkyl or diaryl cyclohexanone oximes to their unsaturated nitriles or other fragmentation products has been well documented in the literature,[1] although exceptions have been reported.[2] This route has been variously labeled as second-order Beckmann, abnormal Beckmann, Beckmann fission, and the Beckmann fragmentation reaction. Other alpha substituents which promote this reaction include: amino, keto, hydroxy, imino, methoxy, and carboxy groups. However, alpha-alkenyl monosubstituted cyclohexanone oximes have not been reported to undergo Beckmann fragmentation reactions. We wish to report that this reaction can take place.

RESULTS AND DISCUSSION

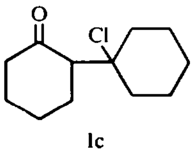
The substituted cyclohexanones employed in this study were 2-(1-cyclohexenyl)cyclohexanone (Ia), 2-cyclohexylcyclohexanone (Ib) and 2-(1-chlorocyclohexyl)cyclohexanone (Ic).



Ia



Ib



Ic

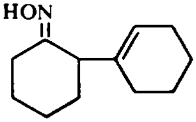
An equilibrium exists between Ia and its conjugated isomer 2-cyclohexylidenecyclohexanone (II) as in Eq. 1.[3] However, II did not form the oxime readily so that no difficulty was encountered in preparing the pure oxime of Ia.

(1)

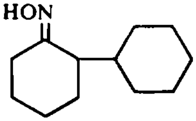
Ia
94%

II
6%

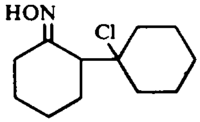
The corresponding oximes (IIa, b, and c) shown below were prepared under neutral conditions using hydroxylamine hydrochloride and sodium acetate. These oximes were examined by NMR, but these data could not establish with any degree of certainty if the *syn*- and/or *anti*-isomer was present. Previous work[4] on the Beckmann rearrangement indicates that the phosphorus pentachloride–diethyl ether system seldom results in isomerization of the oxime portion of the molecule and that in general the lactam formation is brought about by the nitrogen entering the ring *trans* to the initial position of the OH group of the oxime.



IIa

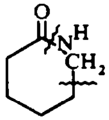


IIb



IIc

The high resolution mass spectra of caprolactam and its N-deuterated analog established a fragmentation pattern for this type structure. The base peak in these spectra was found to be $m/e = 30$ for caprolactam which increased to $m/e = 31$ for the deuterated form. Therefore, this major fragment corresponds to the bond ruptures as in IId with transfer of an additional hydrogen.



IId

By analogy, the high resolution mass spectra of the lactams resulting from the rearrangement of IIa and IIb showed the same bond rupture pattern as in IId. The lactam resulting from the rearrangement of IIc first loses HCl prior to fragmentation so that its mass spectrum is identical to that of IIa.

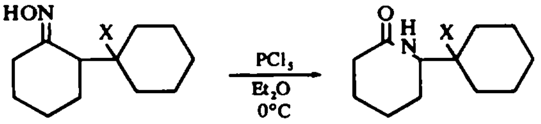
By way of example, the mass spectral data for IVa are given in Table 1.

TABLE 1. HIGH RESOLUTION MASS SPECTRAL DATA FOR 6-AMINO-6-(1-CYCLOHEXENYL)HEXANOIC ACID LACTAM (IVa)

	Measured mass	Calculated mass	Formula
Parent (P)	193·14665	193·1477	$C_{12}H_{19}NO$
P—CO *m/e* 165	165·15212	165·15226	$C_{12}H_{19}N$
Base *m/e* 110	110·09706	110·09697	$C_7H_{12}N$

Therefore, from these data and examination of Fisher–Hirschfelder–Taylor atomic models of these compounds it was concluded that most probably the OH exists in the *anti*-position to the alpha substituents in the oxime structures.

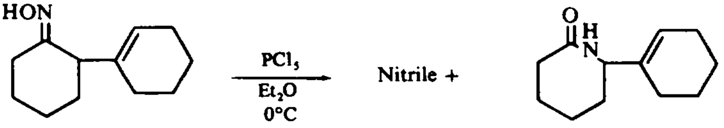
Oximes IIb and IIc undergo the normal Beckmann rearrangement in high yield using phosphorus pentachloride in diethylether as in Eq. 2. Examination of these crude reaction mixtures by IR indicated that fragmentation to nitrile did not occur.



(2)

		% Yield
X=H=IIb	X=H=IVb	90
X=Cl=IIc	X=Cl=IVc	70

The rearrangement of 2-(1-cyclohexenyl)cyclohexanone oxime (IIa) was carried out under similar conditions. However, fragmentation was the predominant reaction in this case. Examination of the oily reaction product by GLC indicated that two peaks constituted 90% of the total. Examination of these two peaks by combined GLC–IR indicated that the major component was a nitrile (III; C≡N, 2240 cm^{-1}) while the other was the lactam (IVa; 3230 and 3280 cm^{-1}; N—H and 1668 cm^{-1}; C=O) as in Eq. 3.

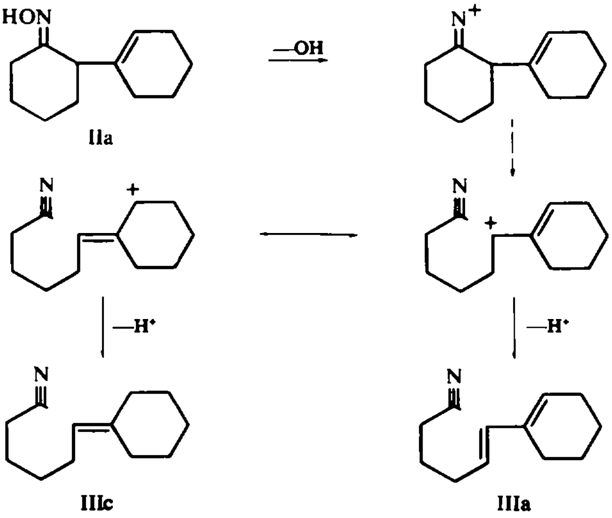


(3)

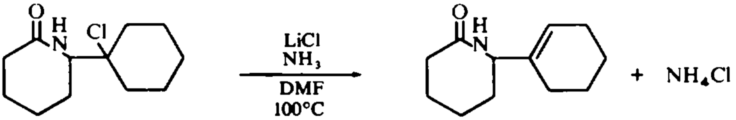
III 65% IVa 25%

A quanitiy of the nitrile was collected by preparative GLC. The UV spectrum in ethanol showed maxima at 229, 237, and 242 mμ, indicating the presence of conjugated double bonds[5] and that possibly nitrile III was a mixture. However, all attempts to effect a separation on III by GLC or TLC were not successful.

It has been shown that fragmentation is favored when the intermediate carbonium ion is resonance stabilized.[1] Thus, it was expected that fragmentation of IIa would result in an allylic carbonium ion which would lead to unsaturated nitriles as shown in the following scheme.



The unsaturated lactam (IVa) was synthesized in high yield by the dehydrochlorination of the chlorolactam (IVc) using lithium chloride, ammonia, and DMF as seen in Eq. 4. This dehydrohalogenation method is a modification of an existing method.[6] The ammonia is required in this reaction to prevent the liberated hydrogen chloride from attacking IVa.



IVc IVa 98% (4)

EXPERIMENTAL

Gas chromatographic analyses and preparative cuts were performed on an F & M Model 720 dual-column chromatograph. The column was ⅛ in × 3½ ft stainless steel packed with 12% Carbowax 20 M on 60–80 mesh HMDS treated Chromosorb W, with a He flow of 40 cc/min. The oven temp was held at 80° for 2 min after sample injection, followed by temp programming at 7·5° per min to 210°.

IR spectra were recorded on a Perkin–Elmer Model 221 spectrophotometer using NaCl optics. UV spectra were obtained in EtOH on a Cary Model 11 recording spectrophotometer.

Synthesis of substituted cyclohexanones and their oximes

Ketones Ia (m.p. 7°; b.p. 130° at 8 mm Hg) and Ic (m.p. 41–42°) were prepared by published methods,[3] while Ib (b.p. 134–35 at 12 mm Hg) was prepared by catalytic hydrogenation of Ia in MeOH over Pt black.

Oximes IIa (m.p. 155–57°) and IIb (m.p. 89–90°) were prepared under neutral conditions and recrystallized from MeOH. The properties of oxime IIc are affected by the choice of the reaction solvent. Oxime IIc prepared using anhyd MeOH had a m.p. of 133–35° (dec) while the one prepared using 17% water in MeOH had a m.p. range of 115–20° (dec). Even so, upon rearrangement, the same lactam (IVc) resulted from each one.

Beckmann Rearrangement Reactions

Rearrangement of 2-cyclohexylcyclohexanone oxime (IIb)

The oxime (1·0 g, 0·005 mole) was dissolved in 50 ml anhyd diethyl ether and cooled to 2° using an ice water bath. The PCl_5 (1·3 g, 0·006 mole) was added to the rapidly stirred oxime soln and allowed to mix 15 min at this temp. The flask was then removed from the bath and the temp allowed to rise slowly to ambient. The reaction was continued an additional hr after which it was cooled to 2°, and ice was added to hydrolyze any remaining PCl_5. The ether layer was removed and the water layer was extracted twice with fresh ether. The combined ether layers were washed once with a small quantity of water, dried over $MgSO_4$, and the ether removed to yield a tacky white semisolid. This was dissolved in a small quantity of MeOH and a white solid was crystallized out at −15°. The solid was vacuum dried for a 90% yield of *6-amino-6-cyclohexylhexanoic acid lactam* (IVb) with m.p. of 134–35°. The structure was verified by IR (Nujol mull), λ_{max} 3230 and 3080 cm^{-1} (N—H) and 1668 (lactam C=O). The mass spectrum, analyzed on the same basis given above for IVa, had M^+ ($C_{12}H_{21}NO$) at $m/e = 195$ and $m/e = 112$ ($C_7H_{14}N$). (Found: C, 73·4; H, 10·3; N, 7·3. $C_{12}H_{21}NO$ requires: C, 73·9; H, 10·8; N, 7·1%).

Rearrangement of 2-(1-chlorocyclohexyl)cyclohexanone oxime (IIc)

A column 25 mm in diam and 1 meter in length was packed with 25 g of solid PCl_5 and washed with diethyl ether. An ethereal soln of the chlorooxime (7·0 g, 0·031 mole; in 350 ml ether) was pulled through the reagent bed at the rate of 10 ml per min using controlled vacuum. The effluent from the column was passed directly into a vacuum flask containing rapidly stirred water at 0°. The vacuum stripped off the excess ether which was condensed in on-line traps. After all the oxime soln had passed through the column, the solid that formed in the water was filtered off. This material was first washed with water, then with ether, and finally vacuum dried to give a white solid with m.p. 185–87° (dec).

Examination of this material by IR and mass spectrometry showed it to be *6-amino-6-(1-chlorocyclohexyl)hexanoic acid lactam* (IVc). The yield was 70% based on starting oxime.

The structure was verified by IR (Nujol mull), λ_{max} 3230 and 3080 cm^{-1} (N—H) and 1668 (lactam C=O). The mass spectrum is identical to that given above for IVa since HCl is first lost to give IVa which then undergoes fragmentation. (Found: C, 62·6; H, 8·7; N, 5·9. $C_{12}H_{20}NOCl$ requires: C, 62·7; H, 8·8; N, 6·1%).

Rearrangement of 2-(1-*cyclohexenyl*)*cyclohexanone oxime* (IIa)

The oxime (1·0 g, 0·005 mole) was dissolved in 100 ml anhyd diethyl ether and cooled to 2° using an ice bath. PCl_5 (1·27 g, 0·006 mole) was rapidly added to the stirred oxime soln. A white ppt formed immediately. The resulting mixture was stirred for 15 min at this temp after which the flask was removed from the bath. After reaching room temp, the ppt (oxime) went into soln and the PCl_5 remained behind. This mixture was allowed to react for 2·25 hr.

The entire reaction mixture was poured over crushed ice to hydrolyze any remaining PCl_5. After this mixture reached room temp, the ether layer was removed and the water layer was extracted once with fresh ether. The combined ether layers were washed twice with small quantities of water, dried ($MgSO_4$), and the ether removed with a N_2 stream yielding a viscous oil. The material balance was 98·3 wt % based on starting oxime.

Examination of this oil by GLC indicated that, in addition to a number of smaller peaks, two peaks constituted 90% of the total sample. An oil, which amounted to 65% of the sample, was identified as III by IR and shown to have conjugated unsaturation by UV spectroscopy. A solid, comprising 25% of the total sample, was identified as IVa (m.p. 111°) by IR and mass spectroscopy. (Found: C, 74·4; H, 9·7; N, 7·2. $C_{12}H_{19}NO$ requires: C, 74·6; H, 9·9; N, 7·3%).

Indirect synthesis of 6-*amino*-6-(1-*cyclohexenyl*)*hexanoic acid lactam* (IVa)

Since the direct rearrangement of IIa to unsaturated IVa cannot be effected in high yields, its synthesis was achieved by dehydrohalogenation of IVc.

The chlorolactam (10·0 g, 0·044 mole) was dissolved in 80 ml DMF contained in a 200-ml, round-bottom flask. LiCl (4·5 g, 0·106 mole) was added and the mixture saturated with ammonia. The flask and its contents were lowered into an oil bath at 100 ± 5°. After mixing vigorously for 5 min, all reactants were in soln.

Ammonia was passed into the reaction mixture continuously from this point to consume liberated HCl. After several min reaction time, NH_4Cl started to precipitate. The reaction was continued for a total of 2 hr, after which the salt was removed by filtration. The dimethylformamide and dissolved ammonia were removed from the filtrate by vacuum distillation (26° at 4 mm Hg) during which time a solid came out of soln. This solid was filtered from remaining liquid and dissolved in 100 ml water and extracted 3 times with 50-ml portions of diethyl ether. The combined extracts were washed twice with small quantities water, dried over $MgSO_4$, and the ether evaporated to yield a nearly theoretical quantity (98%) of the unsaturated IVa m.p. 111°. The NMR spectrum exhibited peaks at 7·0 δ (N—H), 5·4 ($>\mathrm{C{-}H}$), 3·5 ($\mathrm{N{-}CH}<$), 2·2 ($-\mathrm{CH_2{-}C{=}0}$), 1·85 ($-\mathrm{CH_2{-}\overset{|}{C}{=}\overset{|}{C}{-}}$), and 1·3 (aliphatic CH_2).

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