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1-AZABICYCLO-(3.3.1)-NONAN-2-ONE: A TWO CHAIR BICYCLIC LACTAM CONTAINING BRIDGEHEAD NITROGEN

THE UNIVERSITY OF ARIZONA M.S. 1983

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1-AZABICYCLO-[3.3.1]-NONAN-2-ONE:
A TWO CHAIR BICYCLIC LACTAM CONTAINING BRIDGEHEAD NITROGEN

by

Robert Gould Shaw, Jr.

A Thesis Submitted to the Faculty of the
DEPARTMENT OF CHEMISTRY
In Partial Fulfillment of the Requirements
For the Degree of
MASTER OF SCIENCE
In the Graduate College
THE UNIVERSITY OF ARIZONA

1983
STATEMENT BY AUTHOR

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Professor of Chemistry
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TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>LIST OF ILLUSTRATIONS</td>
<td>v</td>
</tr>
<tr>
<td>LIST OF TABLES</td>
<td>vi</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>vii</td>
</tr>
<tr>
<td>1. INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>2. RESULTS AND DISCUSSION</td>
<td>5</td>
</tr>
<tr>
<td>Acid Chloride Route</td>
<td>5</td>
</tr>
<tr>
<td>Aminoacid Route</td>
<td>6</td>
</tr>
<tr>
<td>3. EXPERIMENTAL</td>
<td>14</td>
</tr>
<tr>
<td>2-(3-Piperidine)-Propionic Acid</td>
<td>14</td>
</tr>
<tr>
<td>Reaction with Aqueous Hydrochloric Acid</td>
<td>15</td>
</tr>
<tr>
<td>Reaction with Thionyl Chloride</td>
<td>17</td>
</tr>
<tr>
<td>Reaction with Triethylamine</td>
<td>17</td>
</tr>
<tr>
<td>1-Azabicyclo-[3.3.1]-nonan-2-one (6)</td>
<td>18</td>
</tr>
<tr>
<td>Stability of (6) Toward Water, Acid and Base.</td>
<td>20</td>
</tr>
<tr>
<td>Water, 25°C</td>
<td>20</td>
</tr>
<tr>
<td>Water, 100°C</td>
<td>20</td>
</tr>
<tr>
<td>Aqueous Sodium Hydroxide, 25°C, 100°C</td>
<td>20</td>
</tr>
<tr>
<td>85% Phosphoric Acid</td>
<td>21</td>
</tr>
<tr>
<td>p-Toluene sulfonic Acid Monohydrate</td>
<td>21</td>
</tr>
<tr>
<td>Potassium tert-Butoxide</td>
<td>22</td>
</tr>
<tr>
<td>4. REFERENCES CITED</td>
<td>23</td>
</tr>
</tbody>
</table>
LIST OF ILLUSTRATIONS

Figure | Page
-------|------
1. Mass Spectrum of 1-Azabicyclo-[3.3.1]-nonan-2-one | 8
2. NMR Spectrum of 1-Azabicyclo-[3.3.1]-nonan-2-one | 9
3. Infrared Spectrum of 1-Azabicyclo-[3.3.1]-nonan-2-one (Solid film) | 10
4. Infrared Spectrum of 2-({3-Piperidine) Propionic Acid (KBr pellet) | 16
### LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Effect of Resonance Stabilization on Infrared Carbonyl Absorption of Bicyclic Lactams</td>
<td>11</td>
</tr>
</tbody>
</table>
ABSTRACT

Contrary to popular opinion and in formal disagreement with Bredt's Rule, it has been found that a conformationally strain-free bicyclic lactam containing bridgehead nitrogen is rendered significantly more stable by N-C=O resonance interaction. 1-Azabicyclo-[3.3.1]-nonan-2-one has been synthesized by heating 2-(3-piperidine) propionic acid under high vacuum. The carbonyl infrared absorption of this lactam appears at 1680 cm$^{-1}$ whereas that of the corresponding ketone, bicyclo-[3.3.1]-nonan-2-one is found at 1711 cm$^{-1}$. Stability toward boiling water and p-toluenesulfonic acid in addition to facile polymerization in 85% phosphoric acid and hydrolysis show this lactam to be much more stable than previously predicted.
INTRODUCTION

Until recently, it has been supposed that bicyclic lactams containing bridgehead nitrogen should be very difficult if not impossible to synthesize. In 1938, Lukes pointed this out, stressing the lack of resonance stabilization of the N-C=O moiety in the same manner that Bredt's Rule forbids bridgehead olefins (Bredt et al. 1924). However, this did not deter synthetic chemists from attempting to synthesize these compounds; in 1957, L. N. Yakhontov and M. V. Rubsitov reported the synthesis of 1-azabicyclo-[2.2.2]-octan-2-one (1). However, this has not been widely accepted due to incomplete chemical analysis.

\[\text{N}\]  
(1)

A significant step forward was the synthesis of 2,2-dimethyl- and 2,2,6-trimethyl-2-quinuclidones (2) by Pracejus (1959) by reaction of the corresponding acid chloride amine hydrochloride salt with triethylamine in ether:

\[\text{C}_2\text{H}_5\text{N}^+ \text{H}_2\text{Cl}^- \xrightarrow{(\text{C}_2\text{H}_5)_3\text{N}} \text{N}\]  
(2)
These low-melting solids were found to have unusually high carbonyl infrared absorption frequencies. They are easily hydrolysed in water and show a marked tendency to polymerize.

All of these investigators have stressed the lack of N-C=O resonance interaction as the chief barrier to efficient laboratory synthesis. Indeed, the instability of Pracejus' lactams coupled with the instability of bicyclo-[3.3.1]-nonan-1-ene (3) (Wiseman 1970, Marshall and Faubl 1970), show this to be a well-founded conclusion.

![Diagram](3)

However, conformational strain should not have been overlooked in these early investigations. The conclusions of Prelog (1950; and others 1950) and Fawcett (1950) that only bicyclic systems containing large rings can accommodate bridgehead double bonds seems to bear this out. Accordingly, ring strain and H-H crowding associated with compounds (2) and (3) should be considered as additional contributors to their unusual properties. For example, the polymerizability of 2-azabicyclo-[2.2.2]-octan-3-one (4)

![Diagram](4)

reported by Hall (1960) must be due to its rigid boat conformation since N-C=O resonance is uninhibited in this structure. From these findings,
it may be concluded that the quinuclidones prepared by Yakhontov and Rubsitov (1957) and Pracejus (1959) owe their unusual properties to their strained boat conformations as well as limited resonance stabilization.

In an effort to prepare a more stable bridgehead lactam, Hall and Johnson (1972) reasoned that the presence of an additional nitrogen atom adjacent to the carbonyl carbon should serve to stabilize the bridgehead N-C=O moiety by electron donation. Accordingly, the strainless 2-chair 3-isopropyl-1,3-diazabicyclo-[3.3.1]-nonan-2-one structure (5a) was synthesized.

This bicyclic urea was found to be stable toward boiling water, p-toluenesulfonic acid and phosphoric acid. The infrared carbonyl absorption at 1650 cm\(^{-1}\) further confirms the strainless conformation of this compound.

With the above results, it was surmised that the synthesis of 1-azabicyclo-[3.3.1]-nonan-2-one (6) would shed more light on the relative contributions of resonance stabilization and conformational strain toward the properties of these compounds. With the existence of the highly
strained quinuclidone (2) and the much more stable urea (5a), it was reasoned that structure (6) should demonstrate a degree of stability between these two extremes. Therefore, the synthesis of lactam (6) was chosen as the goal of this study.
RESULTS AND DISCUSSION

Inasmuch as the highly strained quinuclidones (1) and (2) have been obtained in good yield by the acid chloride route (Yakhontov and Rubsitov 1957, Pracejus 1959), this method was deemed the method of choice for the synthesis of the title lactam (6).

**Acid Chloride Route**

Considering the above results, 2-(3-pyridine) acrylic acid was hydrogenated in one step to give 2-(3-piperidine) propionic acid (7):

\[
\text{Reaction of the product with aqueous hydrochloric acid followed by treatment with thionyl chloride gave the hydrochloride salt of the acid chloride (8):}
\]

\[
\text{(7)} 
\]

\[
\text{(8)} 
\]

Reaction of (8) with 2.7 equivalents of triethylamine in both diethyl ether and 1,2-dichloroethane gave an oily crystalline material
after evaporation of solvent. Infrared analysis of this material suggested a mixture of several compounds indicated by a strong broad band at 3320 cm⁻¹ suggesting secondary amine and a complex carbonyl absorption centered at 1670 cm⁻¹. The presence of water is also suspected from a broad band at 3500 cm⁻¹.

The region between 1700 cm⁻¹ and 1200 cm⁻¹ of the infrared spectrum is, however, very similar to the pattern in the spectrum of (6). This similarity together with the crystalline nature of the residue seems to indicate that (6) is one of several products. Several repetitions of these experiments afforded similar results. Existing evidence is insufficient at this time to make any definite conclusions concerning the formation of lactam (6) by this method.

**Aminoacid Route**

Due to the sensitivity of the acid chloride toward moisture and the possibility of simplifying the synthesis by three steps, attention was directed toward the dehydration and cyclization of (7) to give (6) directly:

![Chemical Structures](attachment:image.png)

As a result of many trials, a 7% yield of (6) was obtained as a waxy solid by heating (7) from 180° to 285° under high vacuum. The product was found to be soluble in acetone, 1,2-dichloroethane, ether and water and seems to
be somewhat hygroscopic. Purification by sublimation at room temperature under high vacuum is rapid and affords pure material melting at 79° to 80°.

The major factor contributing to the low yields obtainable by this method seems to be the tendency for aminoacid (7) to polymerize under these conditions. In a previous attempt to synthesize the title lactam by this method (Hall 1960), only the hard, glassy polyamide was obtained. Reaction at higher temperatures was avoided due to the formation of unwanted side products.

The mass spectrum of (6) shown in Figure 1 reveals a parent peak at m/e 139 (Calculated: 139.2). The fragmentation pattern shows loss of C=O at m/e 111 and a base peak at m/e 83 accounted for by loss of CH₂CH₂C=O leaving the positively charged piperidine ring. Further loss of ethylene leaves an ion with m/e 55.

The NMR spectrum of the title lactam reveals a 1-proton signal at 4.2 ppm and a large spike at 2.5 ppm which dominate the otherwise featureless pattern. All thirteen protons were found to absorb between 1.0 and 4.4 ppm downfield from TMS. This spectrum is shown in Figure 2.

The infrared spectrum of (6) shown in Figure 3 shows a carbonyl absorption at 1680 cm⁻¹. E. N. Marvell et al. (1966) report a 2.5 Å distance between C₃ and C₇ of the bicyclo-[3.3.1]-nonane system suggesting a strain-free 2-chair conformation free of H-H crowding (Hall 1960) for compound (6). Inspection of Table I shows a significantly higher carbonyl
Fig. 1. Mass Spectrum of 1-Azabicyclo-[3.3.1]-nonan-2-one
Fig. 2. NMR Spectrum of 1-Azabicyclo-[3.3.1]-nonan-2-one

Spectrum Amplitude: 6.3
Integral Amplitude: 2.5
Spinning Rate (RPS): 28
Solvent: CDCl$_3$

Sweep Time (sec): 250
Sweep Width (Hz): 500
Filter: 1
RF Power Level: 0.1
Fig. 3. Infrared Spectrum of 1-Azabicyclo-[3.3.1]-nonan-2-one (Solid film)
Table I

Effect of Resonance Stabilization on Infrared Carbonyl Absorption of Bicyclic Lactams

<table>
<thead>
<tr>
<th>Structure</th>
<th>C=O Absorption (cm⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(5a)</td>
<td>1650 (Hall and Johnson 1972)</td>
</tr>
<tr>
<td>(6)</td>
<td>1680</td>
</tr>
</tbody>
</table>
| (9)       | 1711 (Marvell et al. 1966)  
           | 1715 (Bailey et al. 1963)  |
| (2)       | 1733 (Pracejus 1959)    |
| (10)      | 1731 (Zbinden and Hall 1960) |
absorption for (9) indicating substantial resonance of (6). In addition, the constant increase of approximately 30 cm\(^{-1}\) between the carbonyl absorption frequencies of (5), (6) and (9) suggests that (5b) and (5c) contribute equally to the stabilization of (5a):

![Diagram of molecules](image)

This is contrary to the assumption that an extra electron donating atom is necessary for the stabilization of this structure (Hall and Johnson 1972).

On the other hand, the approximately equal carbonyl absorption frequencies for compounds (2) and (10) indicate very little resonance stabilization in the highly strained quinuclidone (2). Bearing in mind that resonance stabilization is dependent on effective p-orbital overlap, it seems reasonable to conclude that the flexible, strain-free structures (5a) and (6) owe their lower carbonyl absorptions to the ability of the carbon skeleton to twist and bend for maximum overlap. In contrast, the rigid boat structure of (2) effectively locks the N-C=0 moiety into one position with approximately zero p-orbital overlap. In addition, the carbonyl absorption frequency is elevated slightly above that of the corresponding ketone (10) due to the electron withdrawing nature of nitrogen in the absence of back donation of electrons by resonance.

Compound (6) also shows a stability to water, acid and base intermediate between (5a) and (2). No reaction was observed upon treatment
with boiling water or p-toluenesulfonic acid at 125°. However, oligomerization of this compound occurs immediately on treatment with 85% phosphoric acid. Heating this reaction mixture to 100° results in formation of a hard glassy polymer identical to the polyamide obtained by heating aminoacid (7).

This bridgehead bicyclic lactam thus represents the first bicyclo-[3.3.1]-nonane system known to polymerize and the first which demonstrates significant bridgehead N-C=0 resonance stabilization within a strain-free carbon skeleton. Both the polymerizability of this material and its high carbonyl absorption frequency for tertiary amides (Conley 1972) show this compound to be somewhat more reactive than its straight chain counterparts. As predicted, the title lactam also demonstrates a stability intermediate between the quinuclidone (2) and urea (5a).
EXPERIMENTAL

All infrared spectra were recorded on a PE 710 Spectrophotometer. NMR spectra were taken on a Varian T-60 Spectrometer. Evaporations under vacuum were carried out with a Buchi Rotoevaporator-R apparatus. Melting points were recorded on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. Elemental analyses and mass spectra were obtained from the University Analytical Center at the University of Arizona.

2-(3-Piperidine) Propionic Acid

2-(3-pyridine) acrylic acid (Aldrich #P6620-3, 25 g, 0.17 mole) was mixed with 500 ml water to which were added 5 g 5% Ru/C (Engelhard Industries). This mixture was hydrogenated at an initial pressure of 600 psi H₂. The temperature was then raised to 105° at which point the reaction began as evidenced by loss of pressure. Pressure was raised to 600 psi after dropping to 200 psi and again after dropping to 500 psi. Reaction as indicated by pressure drop was complete in 1 hour, and was continued for a total of 4 hours.

The reaction mixture was filtered by suction yielding a clear, colorless filtrate. The filtrate was evaporated at 45° and 0.2 Torr, giving a clear, colorless syrup. After pumping for 20 hours at 0.5 Torr, acetone (250 ml) was added and the flask vigorously shaken. Crystallization of (7) was complete in 1 hour. The fine, white crystals were isolated by suction filtration and dried for 1 hour at 65° under vacuum.
Yield: 23.35 g (82.7%) m.p. 176.5° - 177°

Analysis Calculated for C₈H₁₅NO₂:  C, 61.12; H, 9.62; N, 8.91
    Found:  C, 61.32; H, 9.76; N, 8.92

The infrared spectrum is shown in Figure 4.

**Reaction with Aqueous Hydrochloric Acid**

Aminoacid (7), 1.5 g (0.01 mole) were placed in a 100 ml round bottom flask and dissolved in 30 ml water. To this solution were added 1.5 ml (0.02 mole) 37.5% aqueous hydrochloric acid. The colorless solution was evaporated at 60° under aspirator vacuum until crystallization began. Immediately, the vacuum was released and the mixture warmed until a homogeneous solution was achieved. The solution was transferred to a beaker after which crystallization occurred within 5 minutes. After storage overnight at 2°, the crystals were isolated by suction filtration and washed with acetone yielding 1.67 g hydrochloride salt.

Yield: 1.67 g (90.5%) m.p. 229° - 230°

Anal. Calc for C₈H₁₆NO₂Cl:  C, 49.61; H, 8.32; N, 7.23; Cl, 18.31
    Found:  C, 49.31; H, 8.37; N, 7.31; Cl, 18.06
Fig. 4. Infrared Spectrum of 2-(3-Piperidine) Propionic Acid (KBr pellet)
Reaction with Thionyl Chloride

\[
\begin{align*}
\text{H}^+ & \quad \text{H}^+ \\
\text{Cl}^- & \quad \text{Cl}^-
\end{align*}
\]

The starting hydrochloride salt 3 g (0.02 mole) was dried for 16 hours over phosphorous pentoxide at 100° and 0.5 Torr. The dry crystals were transferred to a 100 ml round bottom flask which was employed as the receiving vessel in the simple distillation of thionyl chloride from a mixture of 100 ml thionyl chloride and 25 ml triphenyl phosphite. Pure thionyl chloride (60 ml) was distilled at 73° into the receiving vessel containing the starting material. The flask was protected by a drying tube containing calcium sulfate and the mixture stirred for 4 hours at 25°. The resultant colorless solution was evaporated at 35° under aspirator vacuum leaving behind (8) as a white solid. The product was stored over anhydrous ether in a dry nitrogen atmosphere. The infrared spectrum of this material shows two bands at 1780 cm\(^{-1}\) and 1730 cm\(^{-1}\) indicating extreme sensitivity to moisture.

Yield: 2.0 g. (82.1%)

Reaction with Triethylamine
Following Pracejus' procedure (1959) for the synthesis of 2,2-dimethyl-2-quinuclidone (2), 0.66 g (0.0034 mole) (8) were placed in a 50 ml round bottom flask to which were added 20 ml anhydrous ether. The mixture was stirred vigorously for 0.5 hour affording a suspension of very fine crystals of (8). Dry, finely divided sand (1.5 g) was introduced after which 1.2 ml (0.0086 mole) triethylamine were added in one portion under a dry nitrogen atmosphere. After stirring at 25° for 20 hours, the mixture was filtered by suction. The filtrate was evaporated to dryness at 25° leaving an oily, crystalline residue. The infrared spectrum of this material showed a band at 3500 cm\(^{-1}\) attributed to moisture, absorption at 3320 cm\(^{-1}\) due to N-H stretching and a broad carbonyl band centered at 1670 cm\(^{-1}\).

This experiment was repeated in 1,2-dichloroethane; the infrared spectrum then showed complex carbonyl absorption from 1690 cm\(^{-1}\) to 1660 cm\(^{-1}\) and similar bands at 3500 cm\(^{-1}\) and 3320 cm\(^{-1}\).

Both solvents were employed in additional experiments in which the acid chloride was added to the stirring solvent containing triethylamine with no change in the results.

\[ \text{1-Azabicyclo-[3.3.1]-nonan-2-one (6)} \]

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{HO} \\
\text{K} \\
\end{array}
\xrightarrow{180^\circ - 285^\circ} \xrightarrow{0.05 \text{ Torr}}
\begin{array}{c}
\text{N} \\
\end{array}
\]

Aminoacid (7) 1.0 g (0.0064 mole) was dried under vacuum in a 50 ml round bottom flask at 65°. To the flask were fitted two 20 ml
short path distillation flasks in series. To the second flask was fitted a glass tube leading to vacuum. The round bottom flask was placed inside a horizontal Buchi oven. The oven diaphragm was then closed around the neck between sample flask and the first receiving flask. The temperature was raised to 180° in 14 minutes after which a vacuum of 0.05 Torr was applied. Rotation of the sample flask was continued after 170°. After 4 minutes at 180°, the second receiving flask to which the vacuum tube was attached was cooled by bathing it in acetone. Cooling under these conditions was continued for 1 hour. The oven temperature was raised slowly to 285° over 1 hour with continued cooling under a vacuum of 0.05 Torr. After a total of 2.5 hours, the vacuum was released and the two receiving flasks placed immediately under a dry nitrogen atmosphere. In the first flask, attached to the sample flask, had collected a white powder, very hygroscopic and insoluble in ether. In the sample flask was the hard glassy polyamide reported also by Hall (1960). In the second receiving flask was the desired lactam (6). This waxy solid was removed with a spatula and stored under dry nitrogen.

Yield: 70 mg (7%) m.p. 77° to 79°

Analysis Calculated for C₈H₁₃NO: C, 69.03; H, 9.41; N, 10.06

Found: C, 68.20; H, 9.43; N, 9.84

Two successive sublimations at 25° and 0.05 Torr yielded material melting at 79° to 80°; little change was found for the CHN analysis:

Found: C, 68.29; H, 9.14; N, 9.86

After several additional experiments, it was found that significant weight loss of the sample occurred due to sublimation prior to combustion. In an attempt to correct for this discrepancy, a sample was
weighed and placed in the combustion chamber, removed prior to combustion and weighed again. It was determined that 4% of the material was lost during this step. The sample was then analyzed. Assuming the same 4% loss of material, the following analysis was obtained:

Analysis Calculated for C$_8$H$_{13}$NO: C, 69.03; H, 9.43; N, 10.06  
Found: C, 69.65; H, 9.70; N, 10.11

**Stability of (6) Toward Water, Acid and Base**

**Water, 25°**

Lactam (6), 30 mg, was dissolved in 1.0 ml water and left standing at 25° for 22 hours. Anhydrous ether, 1.0 ml, was added by pipette and the mixture vigorously shaken. The top organic layer was transferred to a salt plate by pipette for infrared analysis. The spectrum was identical to that of the starting material.

**Water, 100°**

Lactam (6), 35 mg, was dissolved in 0.5 ml water in an NMR tube. The tube was placed in an oil bath at 100° for 1 hour. The solution was decanted into a vial to which was added 0.5 ml anhydrous ether. The vial was shaken and an infrared spectrum recorded from the residue as before. The spectrum was weak but consistent with that of the starting material indicating complete stability of the title lactam toward water.

**Aqueous Sodium Hydroxide, 25°, 100°**

Sodium Hydroxide pellets, 80 mg, were dissolved in 2.0 ml water. Lactam (6), 35 mg, were dissolved in this solution which was then divided
between two vials. One vial was stored at 25° for 18 hours. Infrared analysis of an ether extract after evaporation of solvent showed very weak, broad absorption at 1680 cm\(^{-1}\) on an otherwise featureless spectrum indicating significant hydrolysis. Heating the other vial to 100° followed by addition of ether and infrared analysis of the organic extract after evaporation showed no carbonyl absorption on a featureless spectrum. Hydrolysis was judged complete by this criterion.

85% Phosphoric Acid

Lactam (6), 35 mg, was placed in a vial to which was added 20 mg 85% phosphoric acid (1 drop) by pipette. After 18 hours at 25°, ether was added to the thick oil and the vial shaken. Infrared analysis of the residue after evaporation of solvent afforded a featureless spectrum with broad absorption at 1640 cm\(^{-1}\) indicating oligomerization of the lactam. In a similar experiment, lactam (6), 50 mg, was treated with 2 mg 85% phosphoric acid. An infrared spectrum of the resultant oil was obtained immediately after mixing. This spectrum was identical to that obtained from the ether extract of this oil indicating that treatment with 85% phosphoric acid results in oligomerization immediately on mixing and does not progress to complete polymerization with a longer reaction time. The remainder of the oil was heated to 100° in 20 minutes and formed a clear, hard polyamide identical in appearance to the polymer obtained by heating aminoacid (7) to 180°.

p-Toluenesulfonic Acid Monohydrate

A few crystals of p-toluenesulfonic acid monohydrate were placed in contact with 20 mg (6). After 18 hours at 25°, infrared analysis of
an ether extract of this mixture after evaporation of solvent showed no reaction. A similar mixture was placed in an oil bath at 125° for 6 hours. Infrared analysis of the residue yielded a spectrum identical to that of the starting material indicating complete stability of lactam (6) toward this reagent.

Potassium tert-Butoxide

Potassium tert-butoxide, 10 mg, was placed in a vial to which were added 20 mg (6). After 18 hours at 25°, an infrared spectrum of an ether extract of this mixture after evaporation of solvent was found to be identical to that of starting material. The remainder of this mixture was heated at 125° for 6 hours in an oil bath. An infrared spectrum obtained in a similar manner was featureless except for a broad band at 3400 cm⁻¹ indicating decomposition under these conditions.
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