Tetrahedron, Vol. 37, pp. 1283 to 1307, 1981
Printed in Great Britain

0040-4020/81/071283-25 $05.00/0
Pergamon Press Ltd.

TETRAHEDRON REPORT NUMBER R106

NITROGEN INSERTION REACTIONS OF BRIDGED BICYCLIC KETONES. REGIOSELECTIVE LACTAM FORMATION

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(*Received in U.S.A.* 21 *April* 1980)

CONTENTS

INTRODUCTION

This critical review of nitrogen insertion reactions of bridged bicyclic ketones leading to bridged bicyclic lactams is based upon reports of the Beckmann[1] and Schmidt[2] rearrangements and modifications of these reactions. The reactive substrates are primarily oximes, azidohydrins, and alkylnitrones from ketones; the catalysts are active acid derivatives, acids, and bases. Major issues are the regioselectivity of nitrogen insertion, especially the tension between methylene and bridgehead methine migrations; the reactivity of substrates; the competition between nitrogen insertion and cleavage processes; and the reaction conditions necessary to obtain synthetically useful yields of insertion products.

The reader is referred to other sources for nitrogen insertions of bridged bicyclic ring systems through reactions of olefins with hydrazoic acid,[3] via azide decomposition,[4] from vicinal nitrosoamines,[5] by amination of bridged bicycloalkanes or their corresponding chlorides,[6] through rearrangements of α-nitrocarbonyl compounds,[7] or from N-chloroamino bridged bicycloalkanes.[8]

I. BICYCLO[2.2.1]HEPTANONES

(A) 2-Oxo-isomers

1. *Parent system*

(a) *Major bridgehead migration.* The regiochemistry of nitrogen insertion resulting from the Beckmann rearrangement of norcamphor oxime **1** can be viewed in historical perspective in Table 1. The earliest reports in a pair of Swiss patents[9,10] (entry 1) of sulfuric acid catalyzed rearrangement of oxime **1** to form 2-azalactam **2**, the product of bridgehead migration, could not be duplicated by later workers. Hall[11] (entry 2) obtained from oxime **1** a liquid whose vpc analysis indicated seven components, each representing from 6 to 29% of the total mixture. In an effort to clarify matters, Fox

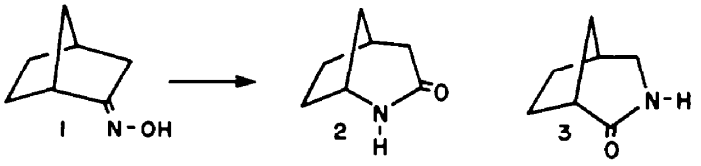


Table 1. Beckmann rearrangement of norcamphor oxime **1**

Entry	Catalyst	Product	Ratio	Yield (%)	Year	Ref.
1	85% H_2SO_4	2	-	70-90	1951,1953	9,10
2	"	seven components			1960	11
3	"	2/3	45/55[a]	15	1968	12
4	25% H_2SO_4	2	-	-[b]	1971	16
5	$PhSO_2Cl$/NaOH	2	-	-	1953	9
6	p-$MePhSO_2Cl$/NaOH	2/3	66/34[c]	38	1960	11
7	$PhSO_2Cl$/NaOH	2	-	-[b,d]	1971	16
8	p-$MePhSO_2Cl$[e]	2	-	35	1961	13
9	ultraviolet light	2/3	-	28	1969	17
10	BF_3/tetrachloroethane	2	-	91	1971	16

(a) The ratio was determined by VPC of the corresponding amines. (b) Mainly nitrile cleavage products were observed. (c) The ratio and structural identities were assumed from VPC analysis and IR of a mixture. (d) Similar results were obtained with PCl_5, polyphosphoric acid, and boron trifluoride/acetic acid catalysts. (e) The oxime tosylate was refluxed in ethanol.

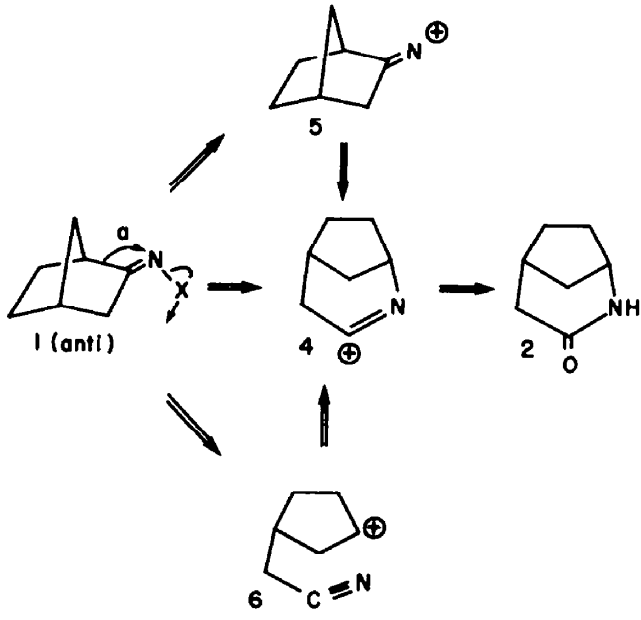
and Reboulet[12] (entry 3) repeated the rearrangement of norcamphor oxime **1** in 85% sulfuric acid and reduced the crude lactam mixture to obtain in low yield a 45/55 ratio of 2-aza/3-azabicyclo[3.2.1]octanes. This result seems to suggest that bridgehead migration during sulfuric acid catalyzed rearrangement of norcamphor oxime **1** is the *minor* process. However, the ratio of amines may not represent the ratio of lactams **2**/**3** formed during Beckmann rearrangement, since the 2-azalactam **2** does not reduce cleanly with lithium aluminum hydride as does the 3-azalactam **3**.[13-15] Under milder acid conditions, Conley[16] (entry 4) obtained mainly nitrile cleavage products, but did find only **2** as lactam product in unspecified yield.

The early Swiss patent[9] report of formation of lactam **2** under conditions of base catalysis (entry 5) also proved to be questionable. Hall[11] (entry 6) treated norcamphor oxime **1** with benzenesulfonyl chloride/aqueous sodium hydroxide to obtain an inseparable mixture, IR consistent with lactam functionality, shown by vpc (vapor pressure chromatography) to be a 66/34 mixture of two major components. Upon the assumption that both components of the mixture were lactams and that the migrating group is "that which forms the stablest carbonium ion," the major lactam was assigned the 2-azalactam structure **2** and the minor lactam the 3-azalactam structure **3**. Conley[16] (entry 7) found

only the 2-azalactam **2** under similar conditions. Elderfield and Losin[13] (entry 8) obtained the 2-azalactam **2** in reasonable (35%) yield by refluxing norcamphor oxime **1** tosylate in ethanol. The structure **2** was so assigned because it was isomeric with the 3-azalactam **3**, obtained independently and correlated with *cis*-cyclopentane-1,3-dicarboxylic acid.

The photochemical Beckmann rearrangement[17] of oxime **1** (entry 9) gave a mixture of lactams **2** and **3**, based upon vpc retention times of the corresponding amines; isomer ratios were not reported. The report[16] that boron trifluoride in tetrachloroethane converts oxime **1** to 2-azalactam **2** in 91% yield (entry 10) is notable for its regioselectivity and high yield.

Major formation of the 2-azalactam **2** regioisomer during Beckmann rearrangement of **1** under the synthetically useful conditions of boron trifluoride catalysis is worthy of mechanistic comment. Alternative pathways are shown in Scheme 1. Norcamphor **1** exists as a mixture of *syn*- and *anti*-isomers.[11] Under conditions of an acid catalyzed equilibrium of oxime stereoisomers, preferential synchronous bridgehead migration of norcamphor *anti*-oxime **1** affords via path a the iminocation **4**, which hydrates to give lactam **2**.



Scheme 1. Possible reaction pathways for rearrangement of oxime **1**

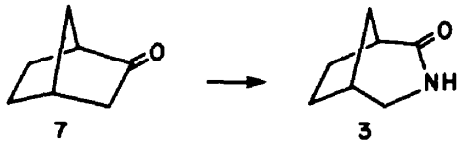
Alternatively, in strongly acidic media carbon migration may be non-synchronous with heterolytic N–X bond cleavage and an electron deficient nitrogen cation **5** may form. Under these conditions migratory preference is not determined by oxime **1** stereochemistry, but by other steric, conformational, or electronic factors. The regioselection for 2-azalactam **2** and the absence of abnormal Beckmann cleavage products[16,18] tend to rule out a nitrogen cation **5** mechanism as a likely explanation for the boron trifluoride in tetrachloroethane results.

Another mechanism involving bridgehead cleavage to **6** followed by recombination of cation and nitrile to give iminocation **4** is possible; however, the absence of abnormal Beckmann cleavage products, nitriles and lactones, normally the major products of norcamphor oxime **1** rearrangements under a cleavage—recombination mechanism, appear to rule out this third pathway.[16,18]

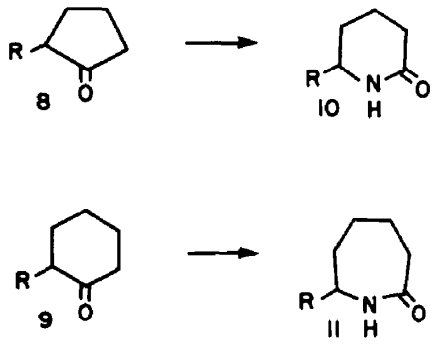
Whatever the mechanism, boron trifluoride in tetrachloroethane affords the most synthetically useful yields of bridgehead migrated 2-azalactam **2**. Yet, in no other case has this reagent been used to catalyze rearrangement of a bridged bicyclic oxime and in this single case there is no detailed experimental section.[16]

(b) *Major non-bridgehead migration.* Elderfield and Losin[13] in 1961 performed the Schmidt reaction on norcamphor **7** with sodium azide and cold concentrated sulfuric acid in chloroform, benzene, or without solvent, to afford 10–30% yields of 3-azalactam **3**. In 1968 Potti and Nobles[14] improved the yield to 40–45% by using hydrazoic acid prepared *ex situ* and adding phosphorus pentoxide to the sulfuric acid. Although to an extent the low yield and the presence of unidentified cleavage products minimize its significance; nevertheless, the preference for solely methylene migrated

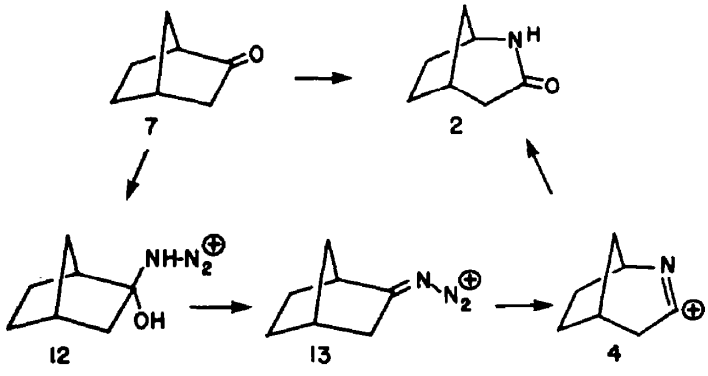
3-azalactam **3** in the Schmidt rearrangement of norcamphor **7** contrasts sharply with the preference for bridgehead methine migration to 2-azalactam **2**, reliably reported by several workers for Beckmann rearrangement of norcamphor oxime **1**. (See IAIb). So, too, does the regiospecificity observed for Schmidt rearrangements of substituted monocyclic ketones **8** and **9** contrast with hydrazoic acid mediated nitrogen insertion in norcamphor **7**. Shechter and Kirk[20] have rearranged



cyclopentanones **8** and cyclohexanones **9** with hydrazoic acid in sulfuric acid to give 60–80% isolated yields of lactams **10** and **11** derived by methine migration.

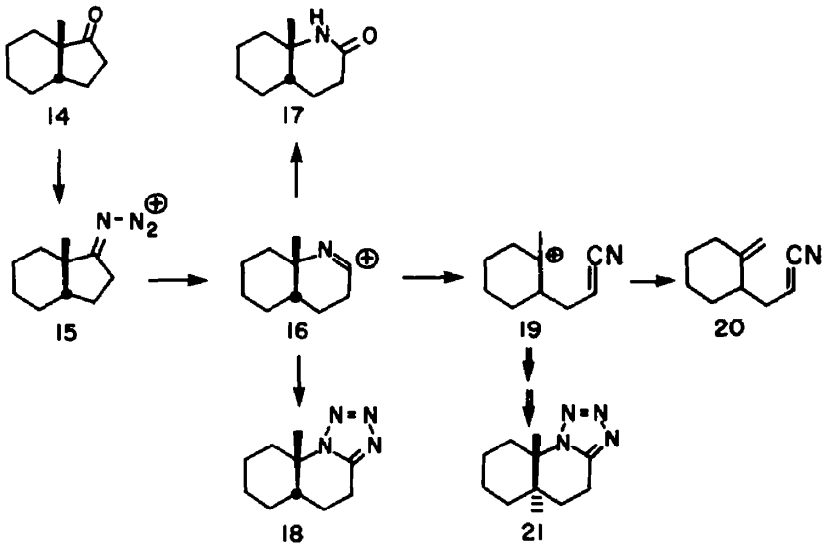


The generally accepted mechanistic views of the Beckmann and Schmidt reactions[13,21,22] in 1961 suggested identical products should result from either rearrangement of norcamphor **7**. In Scheme 2, adapted from Elderfield and Losen,[13] one mechanistic outline for the Schmidt rearrangement of ketone **7** is shown. Following addition of hydrazoic acid to **7** to form an azidohydrin **12**, a loss of water occurs to give the iminodiazonium ion **13**. Ion **13**, analogous to a protonated oxime, is capable of *syn-anti* stereoisomerism, and migration of the group *trans* to the leaving nitrogen would be expected to occur in a synchronous manner. Loss of nitrogen would generate the same iminocation **4**, the precursor of 2-azalactam **2**, formed during the Beckmann rearrangement. But the 2-azalactam **2** is not the observed product, so this mechanistic rationale does not explain preferential formation of the 3-azalactam **3** under Schmidt conditions and primarily 2-azalactam **2** under Beckmann conditions. Why does methylene migrate in the Schmidt reaction?



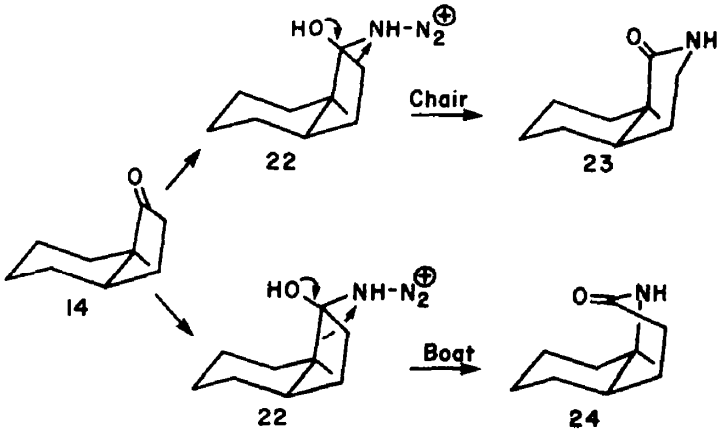
Scheme 2. An iminodiazonium ion mechanism for the Schmidt rearrangement of 7

In 1966 DiMaio and Permutti,[23] drawing upon earlier suggestions of Sauers[24] and of Murray *et al.*[25] on the mechanism of the Baeyer-Villiger reaction, as well as their own work on the Schmidt rearrangement of *cis*-8-methylhydrindan-1-one **14**, suggested the simultaneous action of two mechanisms to explain the formation of regioisomeric nitrogen insertion products. The first mechanism, based upon a stereoelectronic control theory, is that of Scheme 3 and involves stereospecific migration of bridgehead carbon *anti* to the leaving group in the trigonal intermediate **15** to form iminium ion **16**. Addition of water to **16** yields the 2-azalactam **17**, the only lactam formed by this mechanism. For the present argument it is probable that the iminodiazonium ion **15** and the oxime of ketone **14** are isosteric, since $-N_2^+$ is bulkier than OH, and **15** should exist in the *anti* form. The oxime of **14**, which exists only in the stereoisomeric form with hydroxyl *anti* to Me, rearranges with phosphorus pentachloride only by bridgehead migration to give 2-azalactam **17**. Further, it is known that iminodiazonium ions rearrange by *anti* migration as in the Beckmann rearrangement.[23]



Scheme 3. The iminodiazonium ion mechanism for rearrangement of **14**

The mechanism of Scheme 3 for rearrangement of **14** can also be utilized to account for tetrazole **18** formation by addition of azide ion to iminocation **16**, and to explain the formation of nitrile **20** and tetrazole **21**, formed following cleavage of iminocation **16** to carbocation **19**. Under the Schmidt reaction conditions tetrazoles **18** and **21** can not be formed from the corresponding lactam **17** and hydrazoic acid; nor does the unsaturated nitrile **20** form from the lactam **17**, which is stable to the sulfuric acid conditions employed.



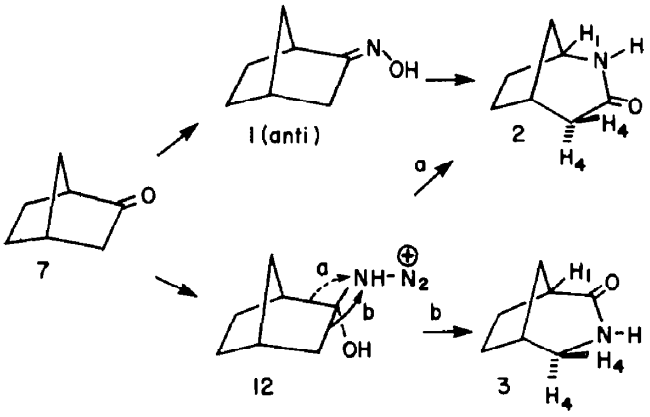
Scheme 4. The azidohydrin mechanism for rearrangement of **14**

A second mechanism for rearrangement of **14** shown in Scheme 4 is based upon a theory of relative boat-chair conformational strain energies. Synchronous rearrangement of an azidohydrin **22** with loss of nitrogen can lead directly to lactams. Two possible azidohydrins are derivable from hydrindanone **14**. If azide is primarily on the less hindered convex face of the molecule as in **22**, and if migration occurs via a transition state with an energetically favored chair conformation,[25] 3-azalactam **23** will result via methylene migration. Bridgehead migration of the same azidohydrin **22** to afford 2-azalactam **24** would occur through a less favorable boat transition state.

In applying the dual mechanistic concepts of Schemes 3 and 4 to the different behavior of norcamphor **7** upon Schmidt and Beckmann conditions, DiMaio and Permutti[26] have suggested that Beckmann rearrangement to afford mainly 2-azalactam **2** is controlled by the preferred *anti* stereochemistry of norcamphor oxime **1**. By contrast, the Schmidt reaction product **3** is determined by the "direction of the attack of reagent (hydrazoic acid) on the substrate **7** and with the duplicity of the mechanism."

However, if the same reasoning utilized in Scheme 4 to explain the preferred methylene migration in the Schmidt rearrangement of hydrindanone **14** is applied to rearrangement of norcamphor **7**, attack by azide on the carbonyl of **7** will occur primarily from the *exo* face to give azidohydrin **12**. The chair conformation transition state formed by path a migration of the bridgehead methine will lead to the 2-azalactam **2**; but this is *not* observed. The 3-azalactam **3** from the boat transition state path b is observed. The suggested boat-chair analysis is clearly deceptive.

Do lactams **2** and **3** exist in chair forms? In so far as lactam functionalities are planar,[27] models indicate semi-rigid half-chair conformations for both the 2-azalactam **2** and the 3-azalactam **3**, differing in the nature of the torsional interactions H_1–NH–CO–H_4 in **2** and H_1–CO–NH–H_4 in **3**. The observed 3-azalactam **3** in the Schmidt rearrangement has a favorable H_1–CO oxygen eclipsing,[28] and the NH and H_4 protons are staggered. The 2-azalactam **2** has an NH–H_1 near eclipsed interaction and the H_4 protons are staggered with the CO oxygen in a less stable arrangement than for **3**. Torsional strain effects appear to favor 3-azalactam **3** as the more stable half-chair structure. But, are these torsional effects felt in the transition states leading from **12** to azalactams **2** and **3**?

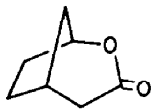


Sauers and Beisler[29] in a 1964 study of oxygen insertion reactions considered forces which might work in opposition to both electronic effects and boat form transition state interactions, which were presumed to favor bridgehead methine migration for norcamphor **7** in the above analyses. The conformation of leaving residue in **12** should not be product determinative, since the N_2 residue should be capable of attaining a *trans* coplanar relationship with either methine or methylene migrating groups. The crucial factor was suggested[29] to be "the torsional strain (of **12**) caused by the eclipsed nonbonded interactions between the substituents on C_2 and the hydrogens on C_3," estimated at 2–3 kcal/mol. Nonbonded interactions between substituents on C_2 and the bridgehead C_1 were said to be less severe since the dihedral angles are 44° (H_1 and C_2 *exo* substituent) and 79° (H_1 and C_2 *endo* substituent; thus, migration of the C_2–C_3 bond would proceed with greater relief of eclipsing strain.

To its credit as a working model, the above localized torsional strain theory, which puts a major focus on relative torsional strain as the determinative transition state energy factor, can be used to

rationalize favored methylene migration not only for the Schmidt rearrangement of norcamphor **7**, but for decomposition of 2-azidonorbornane **25a**,[30] deamination of *exo*- and *endo*-norbornylmethylamines **25b** and **25c**,[31,32] solvolysis of *exo*-norbornylmethyl tosylate **25d**,[33] and reaction of norcamphor with diazomethane via **25e**.[33] The torsional strain theory can not be the total story, however, as can be seen by rearrangement of norcamphor **7** with buffered peracetic or trifluoroperacetic acids, presumably via a tetrahedral intermediate **25f**, to afford only the bridgehead migrated product **26**.[34,35]

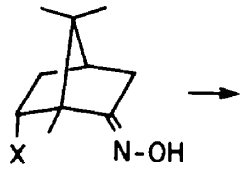
25 a $X=N_3$ $Y=H$
b. $X=CH_2NH_2$ $Y=H$
c. $X=H$ $Y=CH_2NH_2$
d. $X=CH_2OTos$ $Y=H$
e. $X,Y=CH_2N_2^{\oplus}O^{\ominus}$
f. $X,Y=OH,O_2COCH_3(CF_3)$



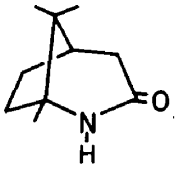
26

2. *Functionalized derivatives*

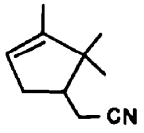
(a) *Major bridgehead migration.* Reaction of camphor oxime **27a** with thionyl chloride,[36–38] sulfuric acid,[39,40] hydroiodic acid,[41] polyphosphoric acid,[42] benzenesulfonyl chloride/sodium hydroxide,[43] phosphorus pentoxide,[44] by photolysis in methanol,[45a] or pyrolysis,[45a] affords no lactam **28**, but only products derived from initial bridgehead cleavage, such as nitrile[45a] **29** and iminolactone[42] **30**. Similarly, the oxime of *endo*-chlorocamphor **27b** upon treatment with sulfuric acid gave only abnormal Beckmann cleavage products.[46] Irradiation of camphor oxime[27a] in methanol/acetic acid has been reported by Sato *et al.*[45b] to afford in unspecified yield a lactam, mp 133–136°, assigned as 2-azalactam **28**. This lactam differs in mp from a lactam, mp 156–160°, prepared by an independent route and also assigned structure **28**.[45c]



27a X=H
b X=Cl



28



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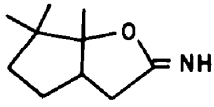
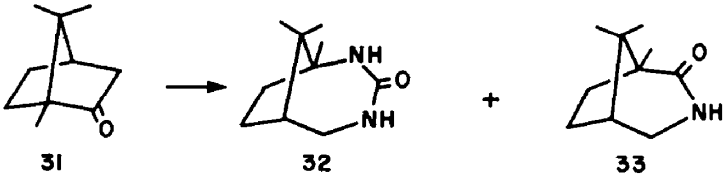


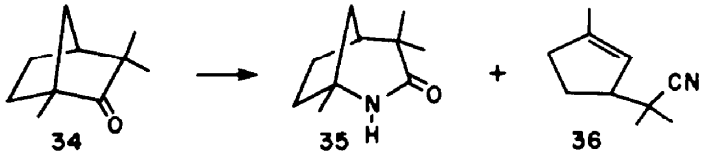
30

Apsimon and Hunter[47a] have reacted camphor **31** with excess sodium azide in chloroform/sulfuric acid to obtain 30% of urea **32**, in principle the product of a bridgehead nitrogen insertion, along with 1% of the 3-azalactam **33**. The authors suggest the urea **32** to be derived by either a second Schmidt reaction of the 3-azalactam **33** or by ring opening of the 3-azalactam **33** to an amino acid, followed by Schmidt reaction to an aminoisocyanate and ring closure. Surprisingly, we[47b] have obtained **33**, the product of methylene migration, in 42% yield from **31** using hydroxylamine-O-sulfonic acid/formic acid, a Beckmann catalyst! (Compare IVA).



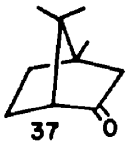
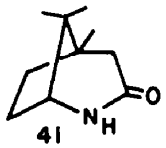
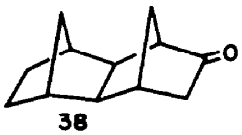
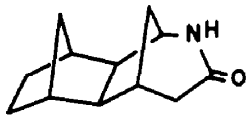
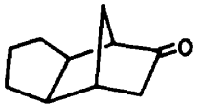
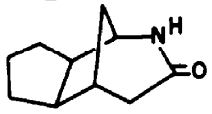
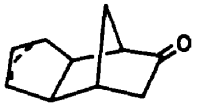
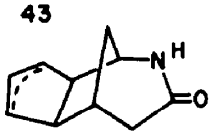
31 32 33

The presence of a bridgehead Me group is not of itself sufficient to cause bridgehead nitrogen insertion to fail under non-photoirradiation conditions. Fenchone oxime **34** upon treatment with phosphorus pentachloride[48] or phosphorus pentoxide[44] affords 2-azalactam **35** in unspecified yield along with olefin cleavage products. It should be noted that treatment of the nitrile **36** with sulfuric acid affords the 2-azalactam **35**.



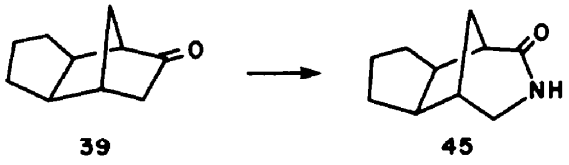
In general oximes of substituted bicyclo[2.2.1]heptan-2-ones having a bridgehead methine hydrogen afford bridgehead nitrogen insertion products. Examples are shown in Table 2; oxime stereochemistry was in all cases unspecified, but is presumably *anti* to the bridgehead.

Table 2. Beckmann rearrangement of substituted norbornan-2-one oximes

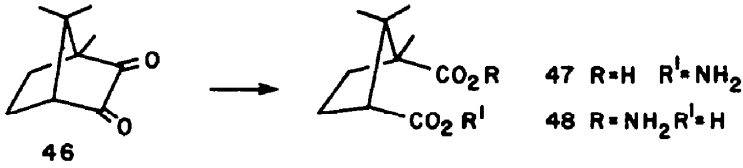
Oxime	Conditions	Product	Yield (%)	Ref.
 37	A	 41	43	50
 38	B	 42	42	11, 51
 39	C,D	 43	15	9
 40	B	 44	31	11, 51

A. Toluenesulfonyl chloride/pyridine; B. Benzenesulfonyl chloride/sodium hydroxide; C. Oxime acetate/hydrochloric acid; D. Oxime acetate/acetic acid.

(b) *Major non-bridgehead migration.* As with the parent norcamphor **7**, Elderfield and Losin[13] found cyclopentanonorcamphor **39** with sodium azide/concentrated sulfuric acid/chloroform undergoes nitrogen insertion to give 3-azalactam **45**, but in less than 10% yield. While camphor **31** afforded only 1% of the 3-azalactam **33**,[47a] and camphorquinone **46** gave only cleavage to camphoramic acid monoamides **47** and **48** with sodium azide/sulfuric acid,[52] camphor **31** with hydroxylamine-O-sulfonic acid/formic acid gave 42% 3-azalactam **33**.[47b] (See IA2a).



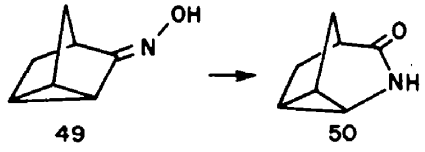
39 45



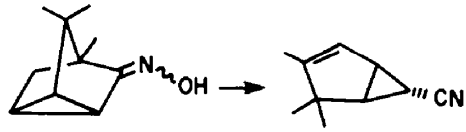
46 47 R=H R'=NH$_2$ 48 R=NH$_2$ R'=H

3. *Bridged tricyclics and polycyclics*

Sharp-melting nortricyclanone oxime **49**, likely a single stereoisomer, was reported by Hall[11] to rearrange with benzenesulfonyl chloride/sodium hydroxide to lactam **50** in 38% yield. Since the structure **50** was assigned on the assumption of cyclopropane ring migration, it should be considered unproven without confirmatory spectral data. By contrast, oxime **51**, the trimethyl analog of **49**, upon treatment with dilute sulfuric acid afforded only nitrile **52**, derived from cleavage of the tertiary bridgehead.[53]



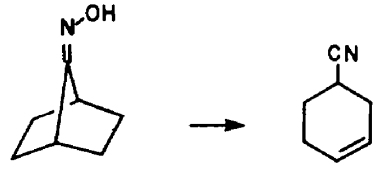
49 50



51 52

(B) 7-Oxo-isomers

Conley and Ghosh,[16] citing unpublished work of Gassman, report phosphorus pentachloride treatment of norbornan-7-one oxime **53** to nearly totally 3-cyclohexenylnitrile **54**. The comment,[16] "These results indicate the generality of the fragmentation process in the bicyclic systems bearing a bridgehead oximino group," should not be taken to imply inability to form lactams from oximes of bridging CO groups, such as in **53**, as will be seen in several sections of this review. (IB, VA, VC, VIIIA).



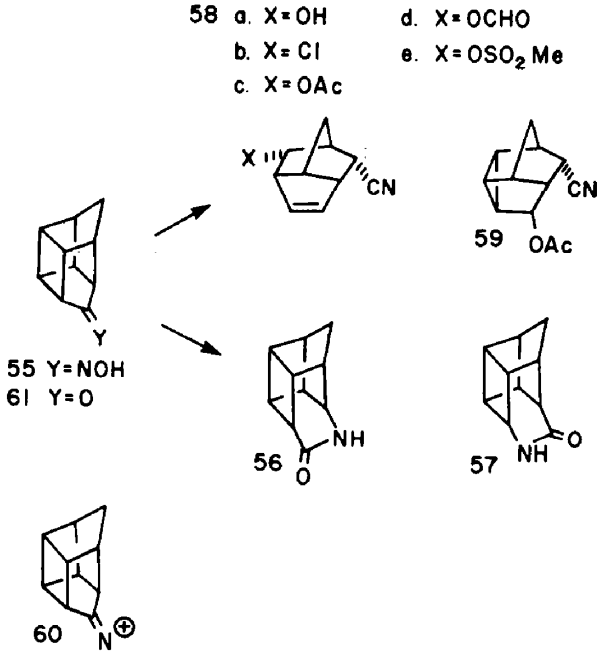
53 54

Hirao *et al.*[19] in 1977 studied nitrogen insertions of a 1:1 mixture of *Z*- and *E*-*bis*-homocubanone oximes **55**. The most effective catalyst for nitrogen insertion was polyphosphoric ester (PPE) in chloroform, conditions not likely to cause *Z*–*E* oxime isomerization. A 47% yield of lactam **56**, from insertion of nitrogen on the cyclopentane side of **55**, and 11% of lactam **57**, from cyclobutane migration, were obtained in addition to 7% of brendanol **58a**, from cleavage of **55** at the cyclobutane

bridgehead followed by cationic rearrangement. Lactam structures **56** and **57** were assigned utilizing ^{1}H NMR spectra of specifically cyclobutane bridgehead deuterated structures.

Other catalysts for rearrangement of oximes **55** were less effective for formation of lactams, but led to greater amounts of cleavage products. For example, aluminum chloride in benzene catalysis led to 60% recovery of brendyl chloride **58b** and acetic acid afforded 40% of a 1:1 mixture of brendanol acetate **58c** and polycycle **59**. Homocubanone **61** with hydrazoic acid in methanesulfonic acid was found by Mehta *et al.*[54] to give only brendanol mesylate **58e** in 45% yield.

The regiospecific fission of homocubanone oximes **55** at only the cyclobutane bridgehead site to form 95% brendanol formate **58d** in a yield unrelated to the configuration of the starting oximes was used by Hirao[19] to suggest a cleavage mechanism involving formation of an unusual cationic nitrogen intermediate **60**, in which oxime stereochemistry has been lost.

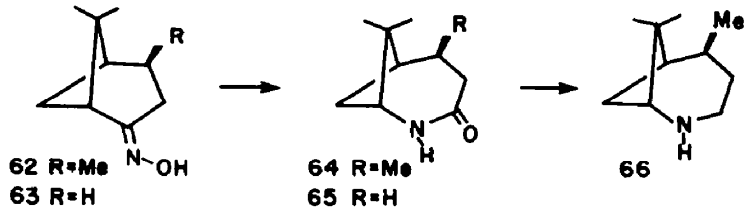


II. BICYCLO[3.1.1]HEPTANONES

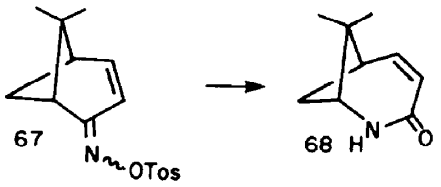
(A) 2-Oxo-isomers

Although nitrogen insertions of the parent ketone have not been investigated, Erdtman and Thoren[50] found verbanone oxime **62** with toluene-sulfonyl chloride/pyridine affords bridgehead inserted 2-azalactam **64**; sulfuric acid catalysis gave only nitrile cleavage products. The structure of lactam **64** and its corresponding amine reduction product **66** follow from ^{1}H NMR shift and coupling parameters and nonidentity with the 3-azaisomer of amine **66**.

Hall[55] isomerized nopinone oxime **63**, assigned the *anti* configuration, with benzenesulfonyl chloride/sodium hydroxide to give 43% yield of what was assumed to be the 2-azalactam **65**. Since **62** is converted to **64**, the 2-azalactam **65** is likely a correct assignment.

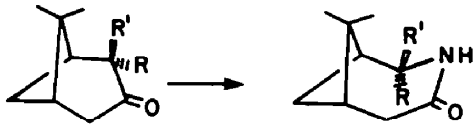


Fleming *et al.*[56] have rearranged pin-2-en-4-one oxime tosylate **67** in acetic acid/hydrochloric acid to give bridgehead substituted lactam 68 in 72% yield (see IVA2).



(B) 3-Oxo-isomers

The oxime of isopinocamphone **69** has been rearranged with either polyphosphoric acid[57] or toluenesulfonyl chloride/sodium hydroxide,[58] to afford lactam **71** in unspecified yield. Pinocamphone **70**, oxime stereochemistry presumably *anti* to the α-Me substituent, afforded with toluene-sulfonyl chloride in unspecified yield the lactam **72** from methine migration.[58]



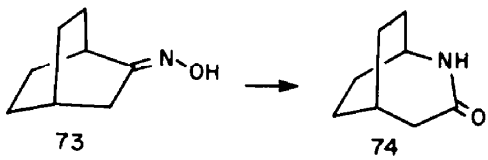
69 R = H , R' = Me ⟶ **71**
70 R = Me , R' = H ⟶ **72**

III. BICYCLO[2.2.2]OCTANONES

(A) 2-Oxo-isomers

1. *Parent system*

Hall[11] rearranged bicyclo[2.2.2]octanone oxime **73** with benzenesulfonyl chloride/sodium hydroxide in 25% yield to what was assigned as the 2-azalactam **74**. Morita and Suzuki[59a] confirmed Hall's assignment obtaining 84% of lactam **74** using oxime **73** and toluenesulfonyl chloride/pyridine catalysis, while Reinisch *et al.*[59b] obtained lactam **74** in 57% yield using polyphosphoric acid catalysis.

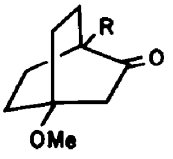
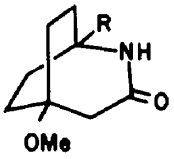
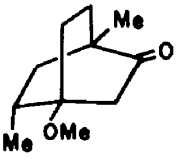
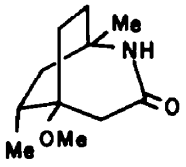
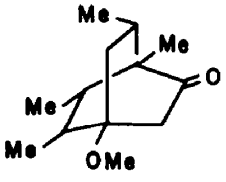
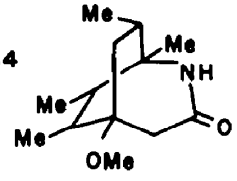


2. *Derivatives and heteroanalogs*

Morita and Suzuki[59a] studied the Beckmann rearrangement of *anti* oximes of the bicyclo[2.2.2]octanones shown in Table 3. In all cases of nitrogen insertion mechanistic precedent for *anti* migration and ^{1}H NMR analysis of products indicated 2-azalactams were obtained. In light of the difficulty in obtaining 2-azalactams from bridgehead substituted nonbornan-2-ones (1A2a), isolation of lactams **81**, **83**, and **84** with nitrogen insertion adjacent to bridgehead are notable. As seen for reaction of **77**, yields of lactam formation decrease with increasing stability of a bridgehead carbocation. Examination of molecular models of the tetramethyloxime **79** revealed it is much more difficult to open than the monomethyl oxime **76** due to steric interactions of the Me groups in **79**. The difficulty in opening the bicyclic oxime **79** to a nitrile cation has been suggested as an explanation for the increased yield of lactam **84** over lactam **81**.

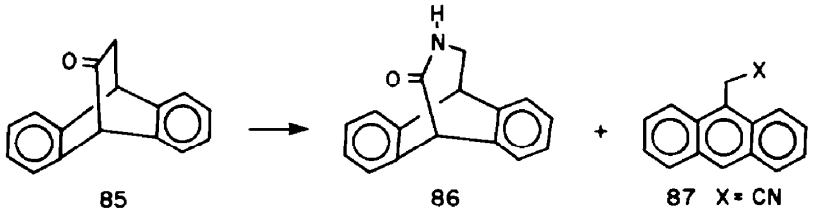
The oxime of dibenzobicyclo[2.2.2]octanone **85** affords only cleavage products, substituted 9-anthranylacetonitriles **87**, with phosphorus pentachloride, thionyl chloride, or benzenesulfonyl chloride/sodium hydroxide; or 9-anthranylacetamides **88** with boron trifluoride, polyphosphoric acid, or hydrochloric acid.[60] By contrast,[61] sodium azide in trichloroacetic acid converted

Table 3. Beckmann rearrangement of substituted bicyclo[2.2.2]octanone oximes[59]

Parent Ketone		Lactam		Catalyst	Yield (%)
75 R=H		80		A (B)	76 (92)
76 R=Me		81		A (B)	23 (27)
				C (D)	6 (2)
77 R=Ph		82		A (B)	0 (0)
78		83		A	23
79		84		A (B)	67 (65)
				C	0

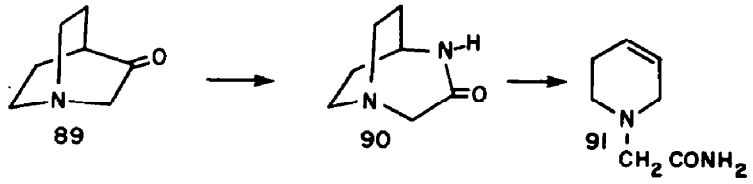
A. Benzenesulfonyl chloride/sodium hydroxide; B. Toluenesulfonyl chloride/pyridine; C. Polyphosphoric acid; D. Phosphorus pentachloride/benzene

dibenzobicyclo[2.2.2]octanone **85** to the 3-azalactam **86** in 10% yield in addition to major amounts of nitrile cleavage product.



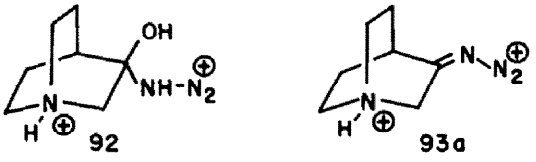
85 86 87 X = CN 88 X = $CONH_2$

Mikhlina *et al.*[62] in a 1965 study of the bridgehead azabicyclo[2.2.2]octanone **89** found nitrogen insertion adjacent to the bridgehead to afford lactam **90** in 50% yield with sodium azide in sulfuric acid and in 28% yield upon treatment of the corresponding oxime of **89** with sulfuric acid. Bridgehead cleavage product **91** was also obtained in 50% and 57% yields, respectively. Lactam **90** could be converted to **91**.

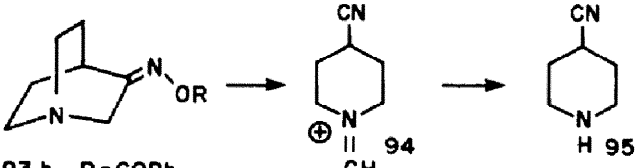


89 90 91 CH_2CONH_2

Although hydrazoic acid catalyzed rearrangement of bicyclo[2.2.2]octanone has not been reported, norbornan-2-one **7** yields the product of methylene migration in the Schmidt rearrangement (IA1b). Paquette and Scott[63] have suggested a decreased proclivity for methylene migration to an electron deficient site in an intermediate of type **92** because of electron withdrawal by a proximal protonated nitrogen atom; stereospecific rearrangement of an *anti*-iminodiazonium ion **93a** is also plausible under the acidic conditions.

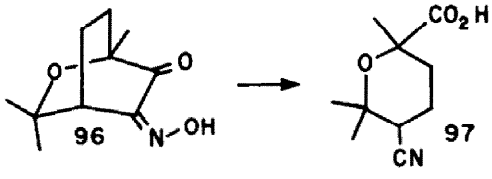


Grob *et al.*[64] upon treatment of the oxime benzoate **93b** with aqueous methanolic potassium hydroxide obtained, naturally, Grob fragmentation. The fragmentation of **93b** involved not bridgehead cleavage as reported[62] for ketone **89**, but methylene cleavage aided by bridgehead nitrogen participation to form the iminium ion **94**, hydrolysis of which gave in 55% overall yield the piperidine **95**. The same fragmentation mode with the oxime tosylate **93c** was observed in 80% ethanol or aqueous base.



93 b R = COPh
93 c R = SO_2 Ph-p-Me

Treatment of the ketoxime **96** with toluenesulfonyl chloride/pyridine gave 91% of cleavage product **97**.[65]



IV. BICYCLO[3.2.1]OCTANONES

(A) 2-Oxo-isomers

1. *Parent system*

Nitrogen insertion reactions of bicyclo[3.2.1]octan-2-one **98** are shown in Table 4. Hall[16] in 1961 reported (entry 1) rearrangement of bicyclo[3.2.1]octan-2-one **98** oxime with benzenesulfonyl chloride/sodium hydroxide to afford in 33% yield crystals, mp 85–87°, assigned the 2-azalactam structure **99** on the assumption of bridgehead migration. Repetition of this work by Szczepanski[66] (entry 2) indicated a mixture of lactams **99** and **100**, with only a slight preference for lactam **99**, results under the base catalyzed conditions. Lactam **99**, mp 115°, was best formed (entry 3) using the hydroxylamine-O-sulfonic acid/formic acid method[66] recently described by Olah and Fung.[67] The slight preference for methine migrated product **99** in the base catalyzed Beckmann rearrangement (entry 2) contrasts sharply with the total preference for bridgehead migrated products in the Beckmann rearrangement of the corresponding bicyclo[2.2.1]heptan-2-one oximes (IA1a and IA2a).

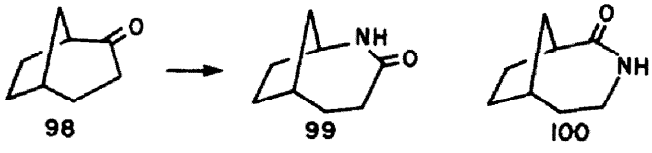


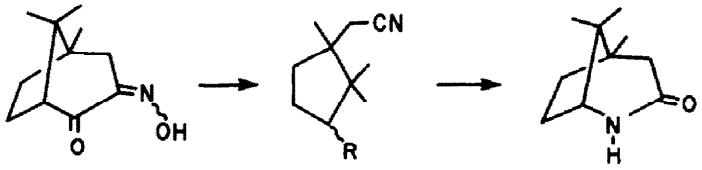
Table 4. Nitrogen Insertions of Bicyclo[3.2.1]octan-2-one **98**

Entry	Derivative	Catalyst	Lactam (%) 99	100	Yield (%)	Ref.
1	Oxime	benzenesulfonyl chloride/ sodium hydroxide	100	-	33	11
2	Oxime	Same	55–60	40–45	48	66
3	-	hydroxylamine-O-sulfonic acid/formic acid	>95	-	73	66
4	-	hydroxylamine sulfate/ sulfuric acid	-	100	36	68
5	-	Same	18–23	77–82	72	66
6	-	hydrazoic acid/sulfuric acid/polyphosphoric acid	-	100	40	68
7	-	Same	33–40	60–67	50	66

Arya and Shenoy[68] (entry 4) treated the ketone **98** with a suspension of hydroxylamine sulfate in concentrated sulfuric acid at 116° to afford a crystalline solid, mp 106°, in 36% yield assigned the 3-azalactam structure **100**. The structural assignment to **100** was made by analogy with the Schmidt reaction product of norbornanone **7** (IA1b) and ^{1}H NMR shift parameters ($CDCl_3$) δ 2.5 (m, C_4, 2 H) and 3.10 (m, C_1, C_9, 3 H). The absence of decoupling data and the suspect assignments suggested a reexamination of this reaction. Szczepanski[66] (entry 5) substituted hydroxylamine hydrochloride for the sulfate salt used by Arya[68] and obtained a crude mixture of 2-azalactam **99**, ^{1}H NMR ($CDCl_3$) δ 3.65 (q, 1 H) and 2.50 (m, 2 H), mp 104°, and 3-azalactam **100**, ^{1}H NMR ($CDCl_3$) δ 3.10 (m, 2 H), 2.50 (m, 1 H); lactam **100** is favored by about a 4:1 ratio.

The ketone **98** in phosphorus pentoxide/sulfuric acid to which hydrazoic acid in chloroform was added (entry 6) was reported[68] to give the 3-azalactam **100** in 40% yield. Szczepanski[66] (entry 7) repeated this reaction and obtained a roughly 2:1 mixture of 3-azalactam **100** to 2-azalactam **99**. It is notable that both the Schmidt and Beckmann rearrangements in strong sulfuric acid give major methylene migrated product, 3-azalactam **100** (entries 4–7). On the other hand, the method of Olah and Fung,[67] also involves catalysis by sulfuric acid and it affords only methine migrated product, 2-azalactam **99** (entry 3).

Fleming[56] converted 5,8,8-trimethylbicyclo[3.2.1]octan-2-one-3-oxime **101** with thionyl chloride to acid chloride cleavage product **102a**. Curtius rearrangement of **102a** to urethane **102b** followed by heating and hydrolysis afforded 61% of lactam 103.



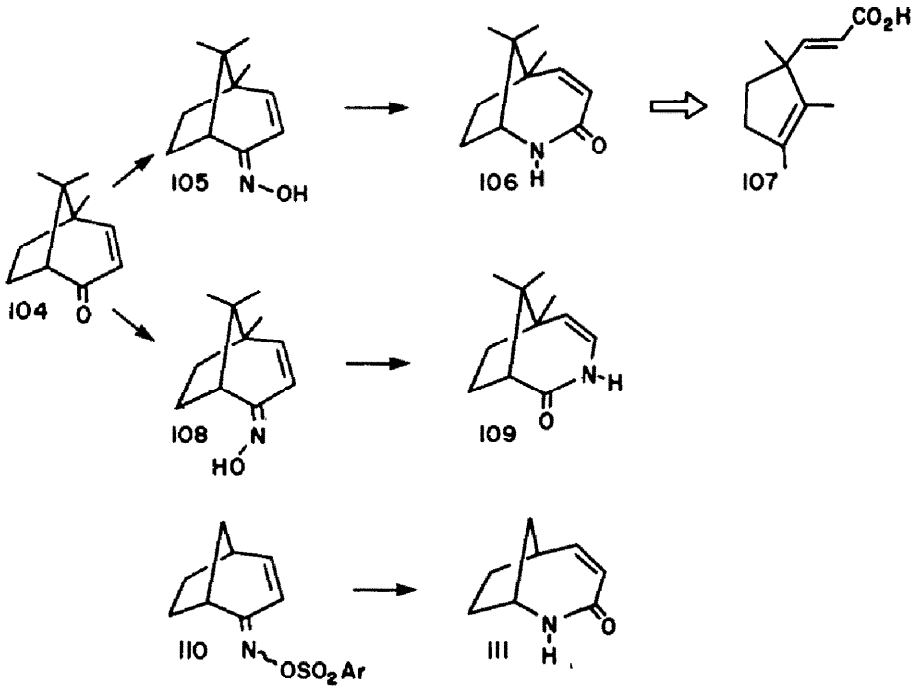
101 102a R = COCl 103

102b R = NHCO$_2$R

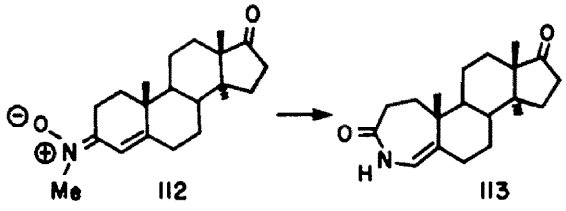
2. *Dehydroderivatives*

A key step in conversion of ketone **104** to cyclopentene **107**, a proposed synthon for a more elaborate Vitamin B_{12} synthetic effort of the Woodward group,[69] involved formation of lactam **106**. Oximation of **104** results in a mixture of **105** and **108**, primarily of the bridgehead *syn* hydroxyl stereoisomer **108**. Polyphosphoric acid treatment of the oxime mixture affords lactams **106** and **109** in an undesirable 1:2 ratio. Ethanol recrystallization of the **105**/**108** oxime mixture gave the desired lactam **106** in 26% yield as well as 57% of recovered *syn* oxime **108**. Fleming and Woodward[69] found the *syn* oxime tosylate from **108** to be thermally stable relative to the *anti* oxime tosylate from **105**, even to base. On this basis, mild acid in a nucleophilic solvent, conditions sufficient to isomerize the oxime tosylate of **108** to that of **105** but to rearrange only the oxime tosylate of **105**, was predicted to give the desired lactam **106**. The mixture of oxime tosylates of **105** and **108** in acetic acid/hydrochloric acid did afford lactam **106** in 82% yield.

Fleming *et al.*[56] also found that the oxime sulfonates **110** underwent rearrangement in acetic acid/hydrochloric acid at 95° to give 2-azalactam **111** in 93% yield.



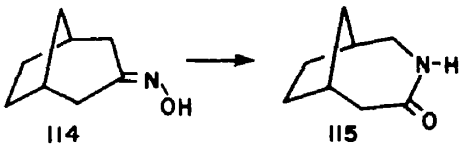
Fleming[69] has suggested that the low propensity for vinyl migration in **108** follows from the inability of the p orbitals of the vinyl group to overlap with the emptying orbital on nitrogen as the tosylate group is lost. When vinyl groups migrate with ease to electron deficient centers in the normal Beckmann rearrangement, it is generally because a new bond can be formed first with the electron deficient N atom.[69,70] In discussing nitrogen insertion adjacent to a vinyl group it is relevant to point out here the observation of Barton *et al.*[71,72] on rearrangements of alkyl nitrones from ketones to N-alkylamides with toluene-*p*-sulfonyl chloride/pyridine. In this alternative to the Beckmann rearrangement there has been found a preference for vinyl migration not related to nitrone geometry. For example, the nitrone **112** rearranges to lactam **113** in 52% yield.



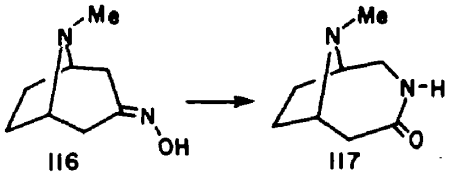
(B) 3-Oxo-isomers

Bicyclo[3.2.1]octan-3-one oxime **114** rearranges with polyphosphoric acid to lactam **115** in 75% yield.[57] N-Methyltropinone **116** undergoes Schmidt rearrangement with hydrazoic acid to lactam **117** in 90% yield.[73]

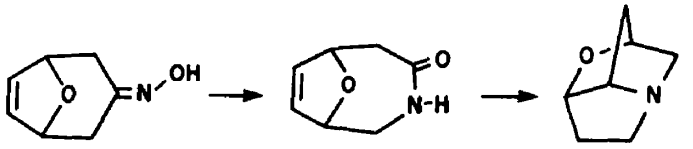
In parallel syntheses of the pyrrolizidine alkaloid hemiloline **120** by Glass *et al.*[74a] and Wilson *et al.*[74b] 8-oxabicyclo[3.2.1]hept-6-en-3-one oxime **118** tosylate was rearranged in ether/potassium hydroxide[74a] or potassium carbonate/aqueous tetrahydrofuran[74b] to give lactam **119** in 68% and 92% yields respectively. Lithium aluminium hydride reduction of **119**, bromine mediated transannular cyclization of the resultant amine, and a hydride removal of halogen afforded hemiloline **120**.



114 115



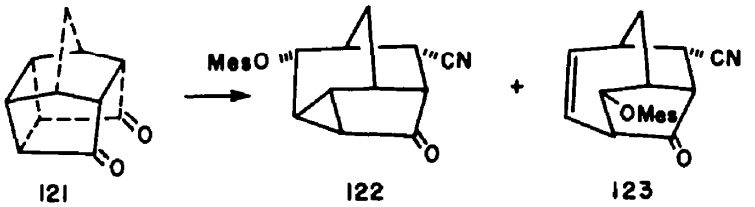
116 117



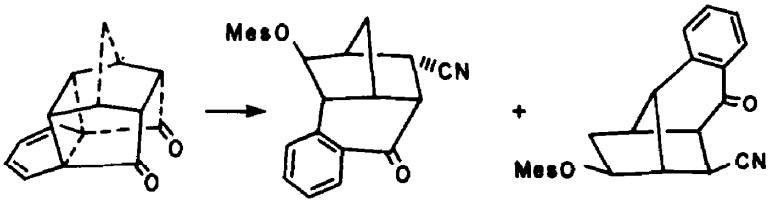
118 119 120

(C) 6-Oxo-isomers

The polycycle **121** is formally a member of the bicyclo[3.2.1]octan-6-one class. Treatment of **121** with methanesulfonic acid/sodium azide yields no nitrogen insertion products, but does give the cleavage—rearrangement products **122** (15%) and **123** (10%).[75a] The polycycle **124** with methanesulfonic acid/sodium azide yields **125** (15%) and **126** (20%), again via cleavage and cationic rearrangement processes.[75b]

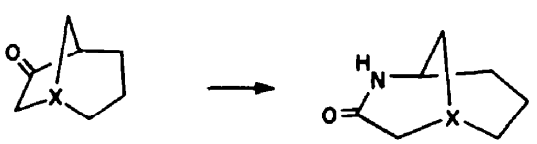


121 122 123



124 125 126

Although the parent bicyclo[3.2.1]octa-6-one has not been studied for nitrogen insertion, the 1-*m*-methoxyphenyl derivative[76] **127a** and the 1-aza analog[62] **127b** have been investigated. The Schmidt reaction of **127a** failed to afford lactam, but the oxime tosylate of **127a** rearranged in 8% yield to lactam **128a**; the oxime of **127b** rearranged with polyphosphoric acid to lactam **128b** in unspecified yield.



127a X = C-Ar
b X = N

128a X = C-Ar
b X = N

V. BICYCLO[3.5.1]NONANONES

(A) 2-Oxo-isomers

While the parent carbobicylic ketone structure has not been subject to nitrogen insertion studies, lactam formation from adamantanone **129**, here considered a 2-oxobicyclo[3.3.1]nonane, has been well studied as shown in Table 5. In addition to formation of lactam **130**, the cleavage products ketomesylate **131**, best formed in 88–90% yield with sodium azide/methanesulfonic acid from **129**,[77] and the oxygen insertion product **132**[78] are to be noted.

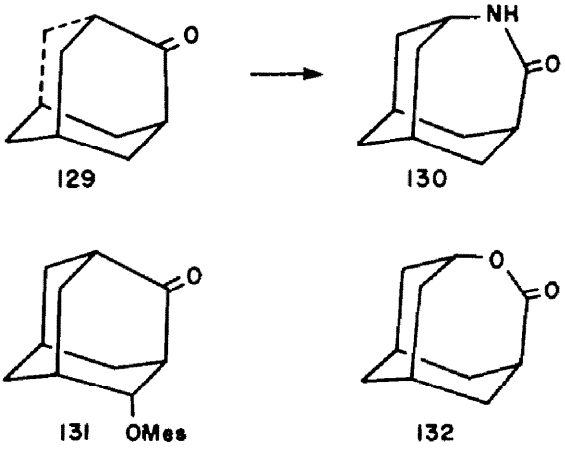
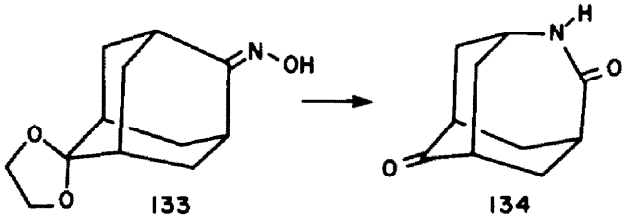


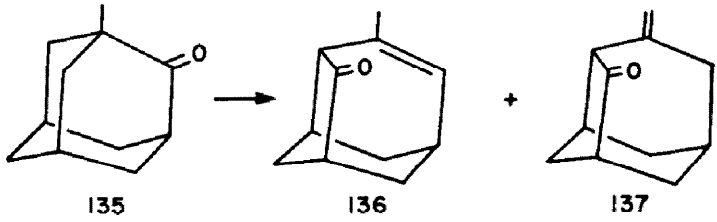
Table 5. Nitrogen insertions of adamantanone **129** to form lactam **139**

Derivative of 129	Catalyst	Yield (%)	Ref.
N-methylimino-N-oxide	toluenesulfonyl chloride/ pyridine/water	70[a]	71
Oxime	polyphosphoric acid	52–57	79–81
	polyphosphoric ester (PPE)	81	82
	hydrochloric acid	40	79
	hydrobromic acid	some	83
	methanol/hv	89	84
Ketone (129)	sodium azide/polyphosphoric acid	23 (70)	81 (85)
	acetic acid/toluenesulfonic acid	31	86
	8:3 methanesulfonic acid/water	36	77, 86
	acetic acid/methanesulfonic acid	70	77
	trifluoroacetic acid	60	77
	trichloroacetic acid	54	77

(a) N-methyllactam derivative of 130

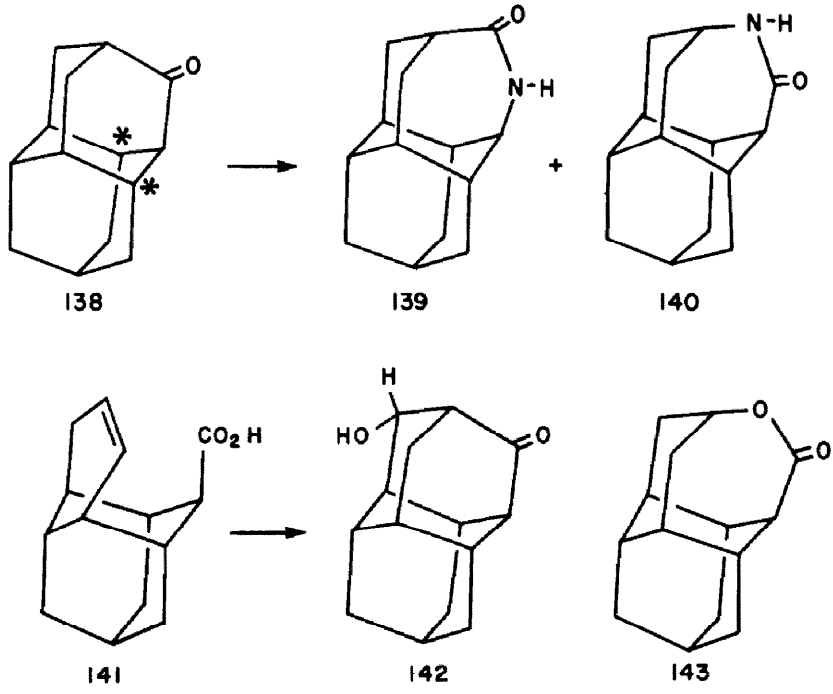
Adamantanone oxime **133** with polyphosphoric acid afforded a 55% yield of ketolactam **134**.[87] However, α-methyladamantanone **135** with sodium azide/sulfuric acid rearranged in 60% yield to a 2:1 ratio of 4-methylprotoadamant-4-en-2-one **136** as major product, and probably 4-methyleneprotoadamantan-2-one **137** as minor product, on the basis of ^{1}H NMR spectral data aided by lanthanide induced shifts.[88] Lactam products from **135** were not reported (see 1A2a).





135 136 137

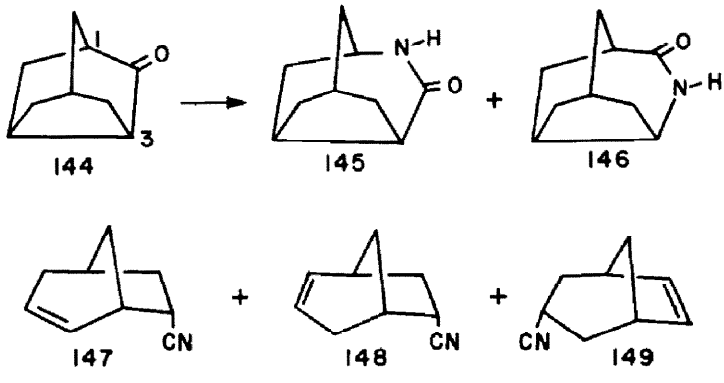
Diamantanone **138** with sodium azide in methanesulfonic acid[89,90] yields 50% of what is postulated to be a mixture of lactams **139** and **140** as well as 41% of acid **141**, a cleavage—hydrolysis product. Cleavage occurs at the bridgehead away from the bulk of the intact adamantyl moiety, since there are no hydrogens diaxial to the leaving group and geometrically favored for elimination at the starred C atoms of diamantanone **138**. Acid **141** with 50% sulfuric acid affords in 82% yield the hydroxy-ketone **142**, stereochemistry speculative, while 96% sulfuric acid converts acid **141** to lactone **143** in 90% yield.



138 139 140

141 142 143

Nitrogen insertion reactions of noradamantan-2-one **144** have been studied by Sasaki *et al.*[91] Mixtures of the two insertion products **145** and **146** are obtained as shown in Table 6. The oxime of **144** exists as a 1:2 mixture of *syn* and *anti* isomers relative to C_1. Varying yields of olefinic nitriles **147–149**, primarily **147** and **148** derived by cleavage at the C_1 bridgehead, were isolated.



144 145 146

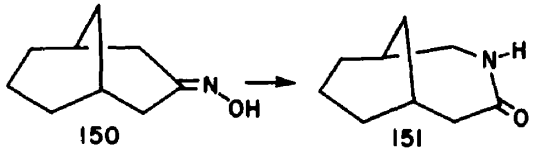
147 148 149

Table 6. Nitrogen insertions into noradamantan-2-one **144**[91]

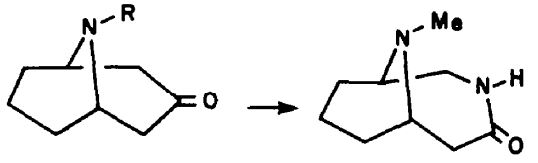
Substrate	Reagent	Yield (%) Lactam 145	Lactam 146
Oxime	polyphosphoric ester (PPE)	42	26
Oxime	toluenesulfonyl chloride/ dimethylformamide	26	1
Oxime	phosphorus trichloride	0.5	1.2
Ketone	sodium azide/methanesulfonic acid/ acetic acid 2/1/9	15	25

(B) 3-Oxo-isomers

Beckmann rearrangement of bicyclo[3.3.1]nonan-3-one oxime **150** with benzenesulfonyl chloride/sodium hydroxide affords 56% yield of lactam **151**,[55] and Schmidt rearrangement of the N-methyltropinone homolog **152a** with hydrazoic acid gives 91% of lactam **153**.[92] The facile Schmidt reaction of **152a** contrasts sharply with the failure of the N-tosyl derivative **152b** to give oxygen insertion product with organic peracids.[93]

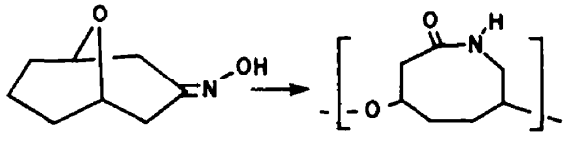


150 **151**



152a R = Me
152b R = SO_2 Ph-p-Me **153**

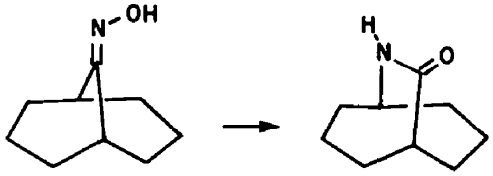
Ogata and Tohoyama[94] obtained only polymeric material, molecular weight 580–650, upon treatment of oxabicyclo[3.3.1]nonan-3-one oxime **154** with the Beckmann catalysts thionyl chloride, benzenesulfonyl chloride, and phosphorus pentachloride. The lactam polyether structure **155** was assigned to the polymer since it lacked amide II bands in the IR spectrum between 1550 and 1600 cm^{-1}, characteristic for *trans* amide absorption expected in a cyclic ether polyamide polymer.



154 **155**

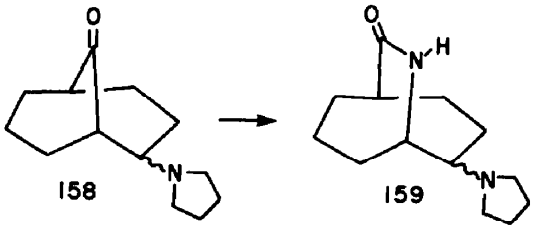
(C) 9-Oxo-isomers

Paquette *et al.*[95] found the oxime of bicyclo[3.3.1]nonan-9-one **156** gives 34% yield of lactam **157** with benzenesulfonyl chloride/sodium hydroxide, indicating that oximes of bridging carbonyls can give nitrogen insertion products (compare IB).



156 **157**

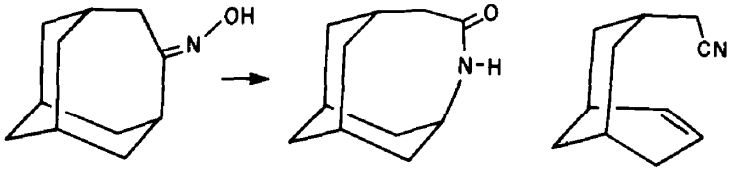
Plostniecks[96] found Schmidt rearrangement of 2-pyrrolidinobicyclo[3.3.1]nonan-9-one **158** with sodium azide/sulfuric acid affords lactam **159** (48/8 *exo/endo*), the product of nitrogen insertion at the bridgehead nearest the amine substituent. If the amine substituent is not directly attached to the carbon having the potentially migrating electron pair, the electron withdrawing effect of the protonated amine does not preclude migration. (Compare rearrangement of **89**). Why the pyrrolidino group should facilitate migration has not been explained.



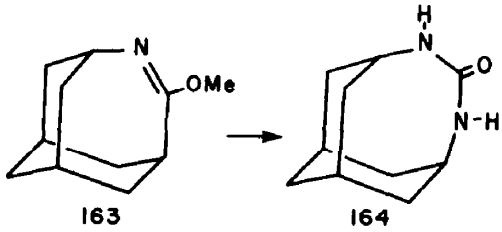
VI. BICYCLO[3.3.2]DECANONES

(A) 9-Oxo-isomers

Sasaki *et al.*[97] observed nitrogen insertion adjacent to bridgehead upon treatment of homoadamantan-4-one anti oxime **160a** (structure shown) with phosphorus pentachloride/ether or toluenesulfonyl chloride/dimethyl formamide to afford lactam **161** in 83% yield; hydrochloric acid, phosphorus pentachloride/chloroform,[98] or polyphosphoric ester/chloroform catalysis led to 56–64% yields of lactam **161**. Extended reaction times with polyphosphoric ester/chloroform reflux led to only nitrile cleavage product **162**, which can form from lactam **161**.[97]



Keiser *et al.*[99] have reported urea formation upon reaction of the iminoether **163** with hydroxylamine/polyphosphoric acid/methanol to afford **164** in 56% yield.



Homoadamantan-4-one **165** upon treatment with sodium azide and various strong acids as shown in Table 6 yields as nitrogen insertion products the lactams **168** and **169**, as well as the corresponding tetrazoles **170** and **171**.[98] The lactams and tetrazoles were reported as 50/50 mixtures of regioisomers on the basis of ^{1}H NMR analysis. The nonstereospecific rearrangement of homoadamantan-4-one **165** to both lactams and tetrazoles in the Schmidt reaction has been explained by assuming a highly energetic cationic species generated by loss of nitrogen from **165b**. This hot species rearranges nonstereospecifically to cations **166** and **167**, which upon addition of water or azide ion gives the observed products. The possibility that the ratio of isomeric diazoiminium

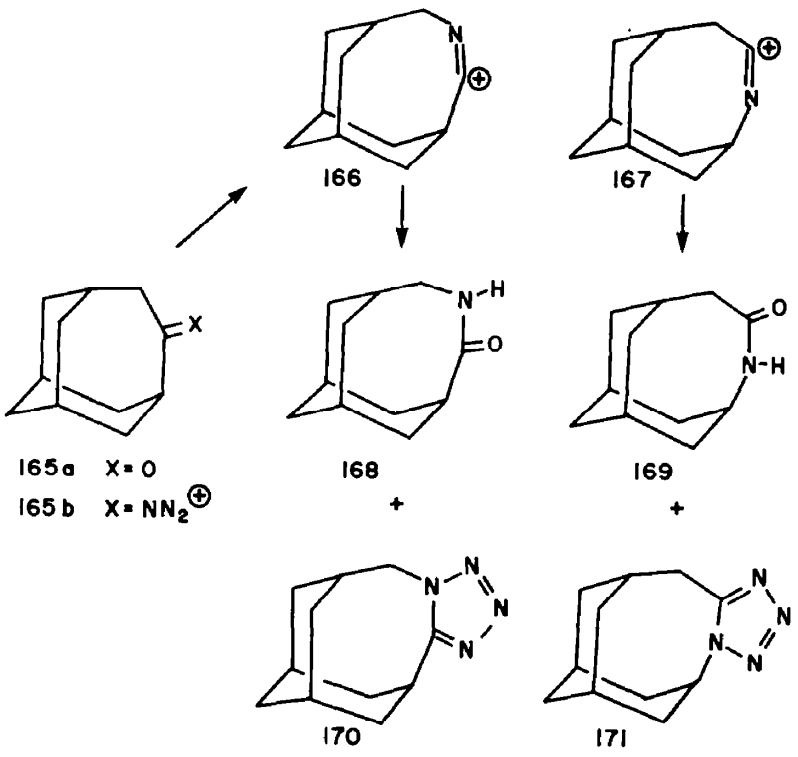
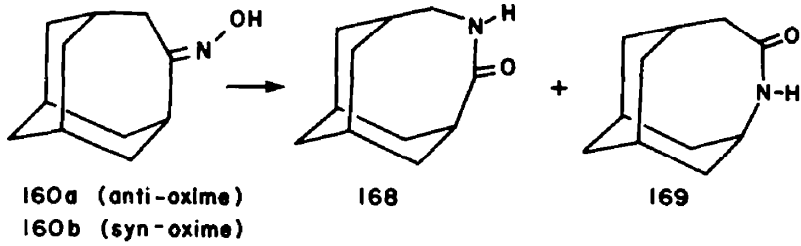


Table 7. Nitrogen insertion of homoadamantan-4-one **165** with hydrazoic acid[98]

Acid catalyst	Yield (%)	
	Lactams 168/169	Tetrazoles 170/171
methanesulfonic acid	7	48
methanesulfonic acid/excess sodium azide	-	93
methanesulfonic acid/acetic acid 1/1	34	24

ions is determinative of product ratios via stereospecific rearrangement has been deemed implausible because of a possible steric preference for one *syn/anti* imine isomer **165b** over the other, and because of the differing lactam ratio for the Beckmann rearrangement of **160** under equilibrating conditions (85% sulfuric acid) (see below) from that in the Schmidt reaction.

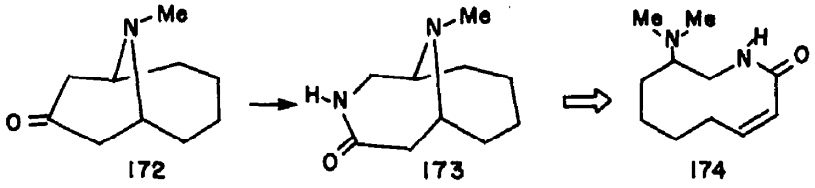
Surprisingly, since insertion of nitrogen adjacent to bridgehead has been reported for Beckmann rearrangement of homoadamantan-4-one oxime **160** with a number of catalysts, the oxime **160** with 85% sulfuric acid at 110° for 12 min gives in 60% yield mainly nitrogen insertion adjacent to methylene.[98] Analysis by ^{1}H NMR indicates a 4:1 ratio of lactams **168** and **169** and no observed cleavage products (cf adamantanone VA). Sasaki *et al.*[98] suggest that under oxime equilibrating conditions using 85% sulfuric acid the *anti* oxime **160a** (OH relative to H_1) leading to **169** has been partially isomerized prior to rearrangement to the *syn* oxime **160b**, which leads to the major product **168**. This unusual propensity for methylene migration during Beckmann rearrangement has also been found for bicyclo[3.2.1]octan-2-one **98** oxime[66,68] (IVA).



VII. BICYCLO[4.3.1]DECANONES

(A) 8-Oxo-isomers

Paquette and Wise[92] rearranged 10-azabicyclo[4.3.1]decan-8-one **172** with hydrazoic acid in 66% yield to lactam **173**, utilized in a study of transannular interactions of medium sized rings. Although the corresponding 8- and 9-membered ring lactams undergo a bridging reaction with acid, lactam **174** fails to undergo intramolecular conjugate addition with acid. The remoteness of the dimethylamino group and β-olefinic carbon in preferred conformations of *cisoid* **174** have been proposed to explain the failure of intramolecular conjugate addition.

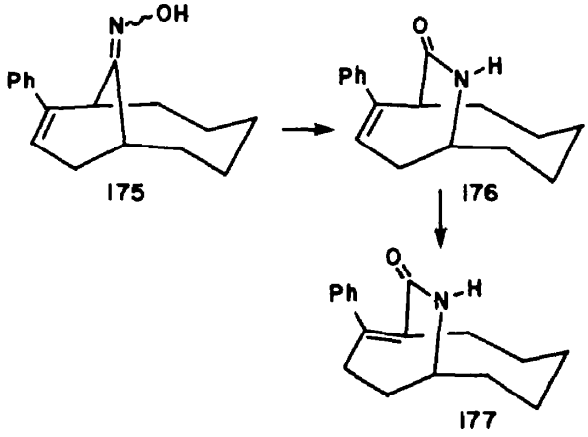


172 173 174

VIII. BICYCLO[5.3.1]UNDECANONES

(A) 11-Oxo-isomers

Buchanan and Jamieson[99] in a study of bridgehead unsaturation in large bicyclic rings looked at the pyridine catalyzed Beckmann rearrangement of the oxime tosylate of 8-phenylbicyclo-[5.3.1]undec-8-en-11-one **175**. Regioselective formation of lactam **176**, derived by migration of the non-allylic bridgehead carbon was observed in 70% yield. Attempted hydrolysis of the lactam **176** with hydrochloric acid isomerized the double bond to the bridgehead olefinic site in lactam **177**.



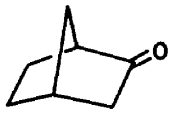
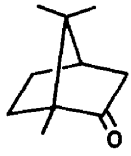
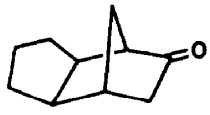
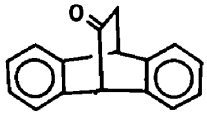
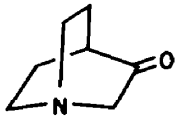
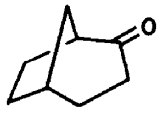
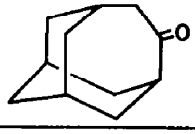
175 176 177

CONCLUSION

Beckmann rearrangements generally occur by preferential bridgehead migration of *E*-oxime stereoisomers to give, if lactams are obtained, nitrogen insertion at the bridgehead. Methylene migration has been observed on occasion upon catalysis with 85% sulfuric acid in several cases,[66,98] and upon reaction of camphor **31** with hydroxylamine-O-sulfonic acid/formic acid.[47b] Polyphosphoric ester or phosphorus pentachloride, high temperatures, or longer reaction times increase the preference for cleavage of *E*-oximes at the bridgehead; bridgehead substitution markedly increases the preference for cleavage, although there are exceptions.[59a]

Schmidt reactions with sodium azide and strong acids, in so far as they occur through tetrahedral reaction intermediates, lead primarily to nitrogen insertion adjacent to methylene rather than bridgehead carbon as shown in Table 8. There are no completely satisfactory rationales for preferential methylene migration.

Table 8. Nitrogen insertion regioselectivity with competitive methylene or bridgehead methine migration. Acid catalysis

Ketone (Section)	Structure	Reagent	Yield (%)	Migrating Group	Ref.
7 I. A. 1. b		NaN_3/H_2SO_4	30	Methylene	13
		$NaN_3/H_2SO_4/P_2O_5$	40-45	Methylene	14
31 I. A. 2. b		NaN_3/H_2SO_4	1	Methylene	47a
		CH_3OH/HOAc/light/ Oxime	-	Bridgehead	45b
		NH_2OSO_3H/HCOOH	42	Methylene	47b
39 I. A. 2. b		NaN_3/H_2SO_4	10	Methylene	13
85 III. A. 2		NaN_3/Cl_3CCOOH	10	Methylene	61
89 III. A. 2		NaN_3/H_2SO_4	50	Methine	62
98 IV. A. 1		NH_2OSO_3H/HCOOH	73	Methine	66
		$NH_2OH \cdot HCl/H_2SO_4$	72	4:1 Methylene	66
		HN_3/H_2SO_4	50	3:1 Methylene	66,
165 VII. A		$NaN_3/MeSO_3H$	93	1:1 Methylene/ Methine	98
		Oxime 160/ 85% H_2SO_4	60	4:1 Methylene/ Methine	98

In light of Shechter *et al.*[100] showing a change in regioselectivity of nitrogen insertion with acid strength for cyclopropyl-alkyl ketones, further investigation of regioselectivity in the Schmidt reaction of azabicyclic ketones is warranted. The use of the Barton *et al.*[71,72] N-alkylnitrone alternative to the Beckmann rearrangement and Olah and Fung's[67] mild one-step conversion of ketones to lactams in high yields with hydroxylamine-O-sulfonic acid/formic acid should be further applied to bridged bicyclic ketones.

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