Syntheses and Configurations of Some Heterocyclic Amidoximes. X-Ray Crystal Structure of 3-Phenyl-5,6-dihydro-2(1*H*)-pyrazinone-*O*-methyloxime

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O-Methyl-α-ketophenylacetohydroximoyl chloride (**1**) was prepared by the reaction of *O*-methyl-α-methoxyphenylacetohydroximoyl chloride (**5**) with *N*-bromosuccinimide and concentrated hydrobromic acid. Reaction of **1** with ethylenediamine gave 3-phenyl-5,6-dihydro-2(1*H*)-pyrazinone-*O*-methyloxime (**6**). 3-Phenyl-5,6-cyclohexano-5,6-dihydro-2(1*H*)-pyrazininone-*O*-methyloxime (**7**) was prepared by reaction of **1** with *trans*-1,2-diaminocyclohexane. The X-ray structure of **6** has been determined. The crystals are orthorhombic, space group Pbca with a = 10.264(3), b = 18.262(4), c = 23.530(4)Å, V = 4411(2)Å^3, and Z = 16. The structure, which was refined to R = 0.038 using 1652 observed reflections, shows the amidoxime moiety to be the *Z* configuration. Reaction of benzohydroximoyl chloride with aziridine gave (*Z*)-aziridinylbenzaldoxime (**16a**). Ultraviolet irradiation of a benzene solution of **16a** gave a mixture of the *Z* and *E* isomers **16a** and **16b**. The *E* isomer **16b** underwent thermal isomerization to **16a** at 100°. Reaction of **16a** with dimethyl sulfate in sodium hydroxide solution gave (*Z*)-*O*-methylaziridinylbenzaldoxime (**17a**). Photoisomerization of a hexane solution of **17a** gave a mixture of the *Z* and *E* isomers **17a** and **17b** which were separated by preparative glc. The isomers **17a** and **17b** are resistant to thermal *Z* ⇌ *E* isomerization. The mechanisms of thermal isomerization of benzamidoximes are discussed.

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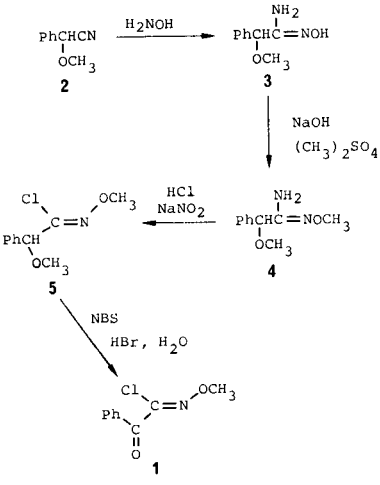
We have recently reported a detailed investigation on the mechanism of amine substitution reactions at the carbon-nitrogen double bond [1]. This paper describes the synthesis by nucleophilic substitution at the carbon-nitrogen double bond of new heterocyclic compounds which contain the amidoxime functional group.

We chose *O*-methyl-α-ketophenylacetohydroximoyl chloride (**1**) as a potential precursor for the preparation of heterocyclic compounds because it contains two functional groups both of which should be capable of reacting with nucleophiles. We also report the synthesis of some configurationally stable amidoximes in which the amide nitrogen is part of an aziridine ring.

Results and Discussion.

The starting material for the synthesis of **1** was α-methoxyphenylacetonitrile (**2**) which can be readily prepared in four steps from benzaldehyde [2,3]. Reaction of α-methoxyphenylacetonitrile (**2**) with hydroxylamine gave the amidoxime **3** (Scheme I). Alkylation of the amidoxime **3** with dimethyl sulfate gave *O*-methyl-α-methoxyphenylacetamidoxime (**4**) which was then converted into the hydroximoyl chloride **5** by nitrosative deamination in the presence of chloride ion [4]. The next step in this synthesis was the transformation of the α-methoxy group into a ketone functional group. This was accomplished in one step by reaction of the hydroximoyl chloride **5** with *N*-bromosuccinimide (NBS) in the presence of a small amount of concentrated hydrobromic acid.

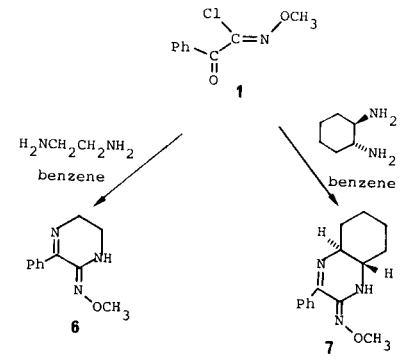
Scheme I



Reaction of the α-ketohydroximoyl chloride **1** with ethylenediamine gave 3-phenyl-5,6-dihydro-2(1*H*)-pyrazinone-*O*-methyloxime (**6**, Scheme II) [5]. Similarly, reaction of **1** with *trans*-1,2-diaminocyclohexane gave 3-phenyl-5,6-cyclohexano-5,6-dihydro-2(1*H*)-pyrazinone-*O*-methyloxime (**7**). A X-ray crystallographic analysis was carried out on **6** which showed that the methoxy group is *anti* to the

phenyl, *i.e.* the molecule is in the *Z* configuration as shown in Figure 1.

Scheme II



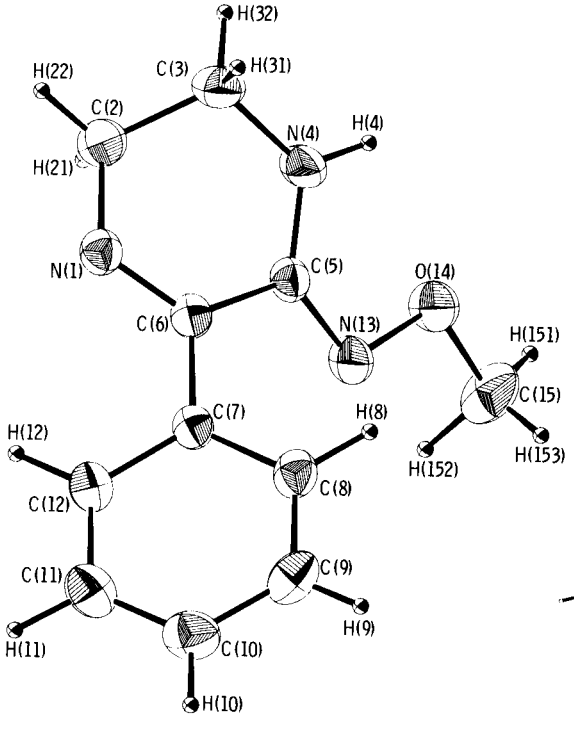
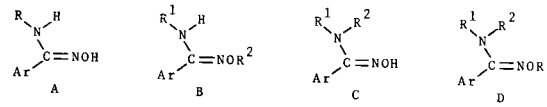


Figure 1. ORTEP view of the molecular structure of **6**. Only one of the two independent molecules is shown, the other being very similar. Thermal ellipsoids are scaled at the 50% probability level. Hydrogen atoms are represented as spheres of arbitrary radii.

Our earlier study [6] suggests that the hydroximoyl chlorides **1** and **5** (Scheme I) have the *Z* configuration about the carbon-nitrogen double bond. Thus, the reaction of the α-ketohydroximoyl chloride **1** gives a substitution product **6** (Scheme II) with retention of configuration which is consistent with our recent observations [1] on reactions of this type. This case, however, is analogous to our previous examples of reactions of hydroximoyl chlorides with primary amines in that product formation is both kinetically and thermodynamically controlled [1]. Since the reaction conditions used for the synthesis of **6** would normally be vigorous enough to cause *Z/E* isomerization of an amidoxime (1, 7-11), we assume that the *Z* configuration of **6** is more stable than the *E* configuration. This fits a general pattern for benzamidoximes (see Table V for a selected group of amidoximes of known configuration) in that the most stable configuration of *N*-alkylbenzamidoximes (Type A and B) is *Z* whereas the most stable configuration of *N,N*-dialkylbenzamidoximes (Type C and D) is *E*.



The *Z* isomer of Type A or B amidoxime probably owes its stability to the fact that the NH moiety can form an intramolecular hydrogen bond to the OH or OR^2 oxygen atom [9,16]. This hydrogen bond is evident in the X-ray structure of **6** as shown in Figure 2, and it has also been found to occur in the crystal structures of amidoximes of structure Type A [13,15]. An exception to the above generalization is the amidoxime **14** (Table V). The bulky phenyl group on the amide nitrogen apparently imparts a large enough steric effect to partially offset the stabilizing influence of the hydrogen bond thereby increasing the amount of *E* isomer in the mixture at thermodynamic equilibrium.

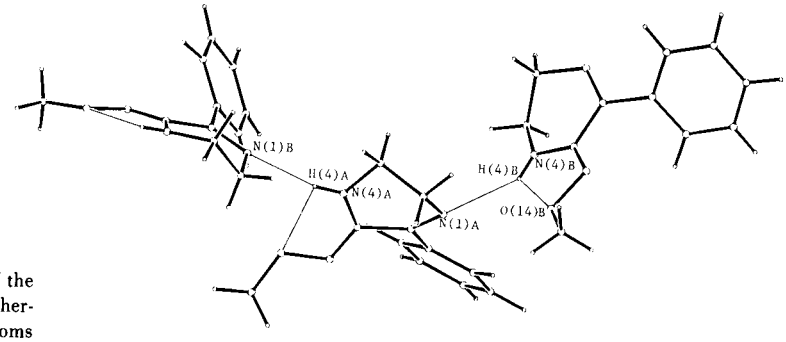


Figure 2. Hydrogen bonding in the crystals of **6**. Atom H(4) is involved in a bifurcated hydrogen bond. The central molecule A is linked to its neighbors B by two intermolecular H-bonds, N(4)A-H(4)A...N(1)B and N(1)A...H(4)B-N(4)B. In both molecules A and B, atoms H(4) also participates in an intramolecular H-bond, N(4)-H(4)...O(14). The relevant geometrical data are given in Table 3.

In Type C amidoximes the most stable isomer generally has the *E* configuration (compound **8** in Table V). If one of

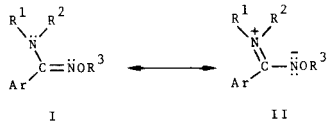
Table 1

Crystal and Experimental Data of **6**.

Chemical formula	$C_{11}H_{13}N_3O$
Formula weight	203.25
Crystal system	orthorhombic
Space group	Pbca
Unit-cell dimensions	a = 10.264(3) Å b = 18.262(4) Å c = 23.530(4) Å V = 4411(2) Å^3
Number of molecules per cell	16
Density (calculated)	1.224 g/cm^3
X-radiation used for data collection	λ(MoKα) = 0.71069 Å
Linear absorption coefficient	0.77 cm^{-1}
Total number of reflections with $3.5 < 2\theta < 45$	2902
Number of reflections with $I > 3\sigma(I)$	1654
Maximum residual electron density	0.12e/Å^3
R factors on observed reflections	R = 0.038 R_w = 0.042
Crystal size	0.73 × 0.24 × 0.18 mm

the substituents on the amide nitrogen of a Type C amidoxime is phenyl (compound **10** in Table V), an equilibrium mixture of the *Z* and *E* isomers is observed [8,9]. Thus, it appears that a *N*-phenyl group in a Type C amidoxime increases the amount of *Z* isomer in the thermodynamic equilibrium, while a *N*-phenyl group in a Type A amidoxime increases the amount of *E* isomer in the equilibrium (compare **12** and **14** in Table V).

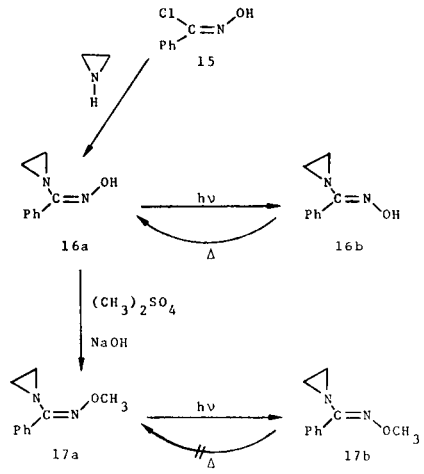
The energy barrier for thermal *Z/E* isomerization of Type A and C amidoximes has been found to be in the range of 20-25 kcal/mole [8,10]. This rather low barrier for isomerization is due to delocalization of the amide nitrogen electron pair which lowers the bond order of the carbon nitrogen double bond (resonance structures I and II).



I II

In order to investigate the effect of decreasing the importance of resonance structure II, we have synthesized the amidoxime **16** (Scheme III) in which the amide nitrogen is part of an aziridine ring. Because of the geometric constraints of the three-membered ring, the amide nitrogen lone pair should be forced away from the plane of overlap with the π-bond in the carbon-nitrogen double bond [17,18].

Scheme III



The amidoxime **16a** was prepared by the reaction of benzohydroximoyl chloride (**15**) with aziridine in the presence of triethylamine. Ultraviolet irradiation (254 nm) of a benzene solution of **16a** gave a mixture of the two isomers **16a** and **16b** as indicated by the apearance of a new peak for the aziridinyl methylene groups in the ^{1}H nmr spectrum of the irradiated sample. The stereochemistry for these isomers could be assigned on the basis of the ^{1}H nmr chemical shifts of the aziridinyl methylene groups, *i.e.* the aziridinyl methylenes were further downfield in the *Z* isomer than in the *E* isomer.

The reaction of benzohydroximoyl chloride (**15**) with aziridine to give the *Z* amidoxime **16a** provides another example of stereospecific addition of amines to benzonitrile oxides [7,19]. Although we were unable to separate isomers **16a** and **16b** by preparative tlc or hplc, we were able to determine their relative stabilities. When a deuterochloroform solution of **16a** and **16b** was heated at 100°, a slow isomerization of the *E* isomer **16b** to the *Z* isomer **16a** was observed ($k = 3.5 \times 10^{-4}$ min^{-1}). To our knowledge this is the only amidoxime of Type C, which does not have a bulky group on the amide nitrogen, where the *Z* isomer is more stable than the *E* isomer. In comparison, the rate constant ($k = 1.3 \times 10^{-2}$ min^{-1} at 100°) of thermal *Z* to *E* isomerization of *O*-methylpiperidinylbenzaldoxime [**21a** and **21b**, Type D amidoxime, R^1 and $R^2 = -(CH_2)_5-$, Ar = C_6H_5] is about 37 times greater than the rate constant for isomerization of **16a** to **16b**.

Alkylation of **16a** with dimethyl sulfate gave the *O*-methyl derivative **17a**. Photoisomerization of the (*Z*)-amidoxime **17a** gave a mixture of the *Z* and *E* isomers **17a** and **17b** which were separated by preparative glc. The *Z* and *E* amidoximes **17a** and **17b** are resistant to thermal isomerization (no change in the ^{1}H nmr spectrum of either **17a** or **17b** on heating at 100° for 6 hours).

Of the many amidoximes of Type C and D where both *Z*

Table 2

Atomic Coordinates and Temperature Factors (anisotropic for non-H and isotropic for H atoms)

Atom	x	y	z	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
N(1)A	0.7199(2)	0.1111(1)	0.2786(1)	0.048(2)	0.045(1)	0.050(2)	0.001(1)	−0.002(1)	0.005(1)
C(2)A	0.7881(3)	0.0705(2)	0.2338(1)	0.061(2)	0.053(2)	0.056(2)	0.003(2)	0.005(2)	0.001(2)
C(3)A	0.9155(3)	0.0410(2)	0.2555(1)	0.050(2)	0.061(2)	0.063(2)	−0.001(2)	0.014(2)	0.003(2)
N(4)A	0.8875(2)	−0.0052(1)	0.3040(1)	0.055(2)	0.062(2)	0.074(2)	0.023(1)	0.019(2)	0.027(2)
C(5)A	0.7902(3)	0.0121(2)	0.3395(1)	0.043(2)	0.042(2)	0.049(2)	0.003(2)	−0.003(2)	0.007(1)
C(6)A	0.7223(3)	0.0829(1)	0.3287(1)	0.040(2)	0.038(2)	0.050(2)	−0.006(1)	−0.003(2)	0.008(2)
C(7)A	0.6545(3)	0.1227(1)	0.3751(1)	0.040(2)	0.034(2)	0.050(2)	−0.004(1)	−0.001(1)	0.009(1)
C(8)A	0.6999(3)	0.1210(2)	0.4309(1)	0.055(2)	0.045(2)	0.054(2)	−0.001(2)	−0.002(2)	0.011(2)
C(9)A	0.6345(4)	0.1599(2)	0.4731(1)	0.086(3)	0.057(2)	0.050(2)	−0.006(2)	0.002(2)	0.008(2)
C(10)A	0.5242(3)	0.1988(2)	0.4602(1)	0.076(2)	0.049(2)	0.074(2)	0.010(2)	0.016(2)	−0.003(2)
C(11)A	0.4782(3)	0.2006(2)	0.4056(1)	0.062(2)	0.063(2)	0.078(2)	0.012(2)	−0.002(2)	−0.003(2)
C(12)A	0.5438(3)	0.1637(2)	0.3632(1)	0.052(2)	0.049(2)	0.057(2)	0.005(2)	−0.006(2)	0.002(2)
N(13)A	0.7457(2)	−0.0281(1)	0.3804(1)	0.057(1)	0.038(1)	0.062(2)	0.010(1)	0.003(2)	0.010(1)
O(14)A	0.8175(2)	−0.0952(1)	0.3801(1)	0.072(1)	0.045(1)	0.075(1)	0.016(1)	0.011(1)	0.014(1)
C(15)A	0.7568(4)	−0.1447(2)	0.4186(1)	0.131(3)	0.043(2)	0.070(2)	0.013(2)	0.015(2)	0.020(2)
N(1)B	0.4018(2)	0.1175(1)	0.8029(1)	0.056(2)	0.051(2)	0.058(2)	0.005(1)	0.016(1)	0.002(1)
C(2)B	0.4464(3)	0.1684(2)	0.7590(1)	0.066(2)	0.069(2)	0.071(2)	0.007(2)	0.035(2)	0.007(2)
C(3)B	0.3364(4)	0.2058(2)	0.7287(1)	0.085(2)	0.062(2)	0.052(2)	−0.005(2)	0.017(2)	0.006(2)
N(4)B	0.2553(2)	0.2401(1)	0.7711(1)	0.065(2)	0.048(2)	0.057(2)	0.008(1)	0.012(2)	0.016(1)
C(5)B	0.2283(2)	0.2047(1)	0.8197(1)	0.035(2)	0.039(2)	0.041(2)	−0.005(1)	−0.001(1)	0.000(1)
C(6)B	0.2990(3)	0.1352(1)	0.8305(1)	0.039(2)	0.043(2)	0.041(2)	0.001(1)	0.001(1)	−0.004(1)
C(7)B	0.2545(3)	0.0846(1)	0.8758(1)	0.046(2)	0.036(2)	0.041(2)	0.001(1)	0.002(2)	−0.003(1)
C(8)B	0.1241(3)	0.0663(2)	0.8825(1)	0.052(2)	0.045(2)	0.043(2)	−0.003(2)	−0.004(2)	−0.001(2)
C(9)B	0.0859(3)	0.0150(2)	0.9224(1)	0.061(2)	0.054(2)	0.058(2)	−0.016(2)	0.005(2)	0.002(2)
C(10)B	0.1770(4)	−0.0171(2)	0.9570(2)	0.086(3)	0.054(2)	0.066(2)	−0.006(2)	0.008(2)	0.015(2)
C(11)B	0.3058(4)	0.0015(2)	0.9517(1)	0.078(3)	0.063(2)	0.060(2)	0.012(2)	−0.006(2)	0.014(2)
C(12)B	0.3447(3)	0.0515(2)	0.9109(1)	0.050(2)	0.057(2)	0.057(2)	0.008(2)	0.003(2)	0.002(2)
N(13)B	0.1546(2)	0.2282(1)	0.8604(1)	0.048(1)	0.040(1)	0.054(2)	0.005(1)	0.000(1)	−0.002(1)
O(14)B	0.1048(2)	0.2981(1)	0.8436(1)	0.064(1)	0.049(1)	0.071(2)	0.019(1)	0.009(1)	0.004(1)
C(15)B	0.0378(4)	0.3283(2)	0.8908(2)	0.100(3)	0.071(2)	0.093(3)	0.037(2)	0.004(2)	−0.014(2)
H(21)A	0.732(2)	0.032(1)	0.222(1)	0.051(7)					
H(22)A	0.805(3)	0.106(2)	0.201(1)	0.072(9)					
H(31)A	0.975(2)	0.082(1)	0.267(1)	0.059(8)					
H(32)A	0.963(2)	0.009(1)	0.226(1)	0.071(9)					
H(4)A	0.938(2)	−0.043(1)	0.313(1)	0.055(8)					
H(8)A	0.781(2)	0.093(1)	0.441(1)	0.048(7)					
H(9)A	0.665(2)	0.158(1)	0.509(1)	0.068(8)					
H(10)A	0.483(2)	0.229(1)	0.490(1)	0.065(8)					
H(11)A	0.397(3)	0.229(2)	0.394(1)	0.088(10)					
H(12)A	0.511(2)	0.166(1)	0.323(1)	0.055(8)					
H(151)A	0.794(3)	−0.191(2)	0.411(1)	0.100(11)					
H(152)A	0.652(4)	−0.147(2)	0.410(2)	0.154(16)					
H(153)A	0.775(4)	−0.128(2)	0.457(2)	0.152(16)					
H(21)B	0.510(4)	0.202(2)	0.776(2)	0.129(13)					
H(22)B	0.493(3)	0.142(1)	0.733(1)	0.070(9)					
H(31)B	0.287(3)	0.167(2)	0.706(1)	0.084(10)					
H(32)B	0.367(2)	0.244(1)	0.705(1)	0.064(8)					
H(4)B	0.214(2)	0.281(1)	0.765(1)	0.063(8)					
H(8)B	0.058(2)	0.090(1)	0.860(1)	0.055(8)					
H(9)B	−0.003(3)	0.004(2)	0.924(1)	0.076(9)					
H(10)B	0.148(3)	−0.054(2)	0.985(1)	0.081(9)					
H(11)B	0.371(2)	−0.018(1)	0.976(1)	0.071(9)					
H(12)B	0.435(2)	0.063(1)	0.908(1)	0.046(7)					
H(151)B	0.021(3)	0.376(2)	0.878(1)	0.093(10)					
H(152)B	0.098(3)	0.330(2)	0.924(1)	0.105(11)					
H(153)B	0.000(5)	0.303(3)	0.898(2)	0.190(19)					

The expression for the thermal parameters with U values in Å^2 is:

$$T = \exp[-2\pi^2(U_{11}h^2a^{*2} + U_{22}k^2b^{*2} + U_{33}\ell^2c^{*2} + 2U_{12}hka^*b^* + 2U_{13}h\ell a^*c^* + 2U_{23}k\ell b^*c^*].$$

Table 3

Bond Lengths (Å) and Bond Angles (°)
E.s.d.'s in Parentheses

Bond Lengths

Atoms	Molecule A	Molecule B
N(1) - C(2)	1.467(4)	1.463(4)
N(1) - C(6)	1.287(3)	1.280(3)
C(2) - C(3)	1.504(4)	1.500(5)
C(3) - N(4)	1.448(4)	1.442(4)
N(4) - C(5)	1.340(4)	1.343(3)
C(5) - C(6)	1.491(4)	1.484(3)
C(5) - N(13)	1.294(4)	1.294(3)
C(6) - C(7)	1.485(3)	1.483(3)
C(7) - C(8)	1.394(4)	1.388(4)
C(7) - C(12)	1.389(4)	1.380(4)
C(8) - C(9)	1.393(5)	1.383(4)
C(9) - C(10)	1.371(5)	1.371(5)
C(10) - C(11)	1.369(4)	1.371(5)
C(11) - C(12)	1.379(4)	1.384(5)
N(13) - O(14)	1.430(3)	1.431(3)
O(14) - C(15)	1.423(4)	1.418(5)

Bond angles

C(2) - N(1) - C(6)	116.6(2)	117.1(2)
N(1) - C(2) - C(3)	110.6(2)	112.9(3)
C(2) - C(3) - N(4)	107.7(2)	107.7(3)
C(3) - N(4) - C(5)	120.1(2)	119.9(2)
N(4) - C(5) - C(6)	116.5(2)	117.2(2)
N(4) - C(5) - N(13)	126.4(3)	126.3(2)
C(6) - C(5) - N(13)	117.0(3)	116.3(2)
N(1) - C(6) - C(5)	120.8(2)	122.1(2)
N(1) - C(6) - C(7)	118.0(2)	117.5(2)
C(5) - C(6) - C(7)	121.2(2)	120.4(4)
C(6) - C(7) - C(8)	121.7(2)	121.9(2)
C(6) - C(7) - C(12)	119.9(2)	119.8(2)
C(8) - C(7) - C(12)	118.4(3)	118.2(3)
C(7) - C(8) - C(9)	119.9(3)	120.9(3)
C(8) - C(9) - C(10)	120.3(3)	119.9(3)
C(9) - C(10) - C(11)	120.3(3)	119.8(4)
C(10) - C(11) - C(12)	119.9(3)	120.3(3)
C(7) - C(12) - C(11)	121.1(3)	120.7(3)
C(5) - N(13) - O(14)	107.5(2)	107.5(2)
N(13) - O(14) - C(15)	108.4(2)	107.7(2)

Hydrogen bonding

Hydrogen bonding atoms	Distances		Angles
A-B...C	A...C	B...C	A-B-C
N(4)A-H(4)A ... N(1)B	2.981(3)	2.15(2)	155(2)
N(4)B-H(4)B ... N(1)A	2.981(3)	2.21(2)	146(2)
N(4)A-H(4)A ... O(14)A	2.535(3)	2.21(2)	101(2)
N(4)B-H(4)B ... O(14)B	2.533(3)	2.20(2)	102(2)

and *E* isomers are known [1,7-9], amidoxime **17** is the only one where the isomers can be separated by a chromatographic method. Isomerization of amidoximes on silica gel has been reported [7,11,20] and is due presumably to acid-catalysis from the SiOH groups on silica gel. It appears

Table 4

Selected Torsion Angles (°) with e.s.d.'s in Parentheses

Atoms	Molecule A	Molecule B
N(1) - C(2) - C(3) - N(4)	57.9(3)	54.4(3)
C(2) - C(3) - N(4) - C(5)	-35.2(3)	-41.3(3)
C(3) - N(4) - C(5) - C(6)	-4.7(4)	8.1(3)
C(3) - N(4) - C(5) - N(13)	171.8(3)	-178.1(2)
N(4) - C(5) - C(6) - N(1)	25.8(4)	16.1(3)
N(4) - C(5) - C(6) - C(7)	-154.7(2)	-166.1(2)
N(4) - C(5) - N(13) - O(14)	-1.2(4)	1.3(3)
C(5) - C(6) - N(1) - C(2)	-0.7(4)	-1.1(4)
C(5) - C(6) - C(7) - C(8)	33.3(4)	45.5(4)
C(5) - C(6) - C(7) - C(12)	-147.6(3)	-137.7(3)
C(6) - N(1) - C(2) - C(3)	-41.3(3)	-35.0(3)
C(6) - C(5) - N(13) - O(14)	175.3(2)	175.1(2)
N(1) - C(6) - C(7) - C(8)	-147.3(3)	-136.6(3)
N(1) - C(6) - C(7) - C(12)	31.9(4)	40.1(4)
C(5) - N(13) - O(14) - C(15)	-170.8(2)	-172.6(2)

that protonation of the nitrogen in the carbon-nitrogen double bond of **17a** and **17b** is not nearly as facile as it is in other amidoximes. This must be a consequence of the electron pair on the amide nitrogen being less available for stabilization of the positive charge on the protonated nitrogen.

Because all the protons on the amidoxime functional group in a Type D structure have been replaced by alkyl groups, the only thermal isomerization pathway available to the compound is torsion (or nitrogen inversion) about the carbon-nitrogen double bond axis. Based on our observation with **17a** and **17b**, it appears that the activation energy for thermal isomerization of an amidoxime in which the amide nitrogen is part of an aziridine ring is rather high, possibly greater than 30 kcal/mole (the value determined for thermal isomerization of phenyl 2-pyridyl ketoxime is 32 kcal/mole [21]). Although we are unable at this time to describe a definitive mechanism for the thermal isomerization of **16b**, we suggest that it does not isomerize by torsion about the carbon-nitrogen double bond of the neutral species. It is possible that **16b** is undergoing isomerization by tautomerism to a nitrone intermediate (**18a** → **18b** in Mechanism I). Other possible mechanisms include isomerization through tautomerism to a nitroso intermediate (**19**, Mechanism II) and self-protonation to give a protonated amidoxime **20a** which isomerizes to **20b** by torsion about the carbon-nitrogen double bond (Mechanism III) [8]. The nitroso mechanism (Mechanism II) seems most likely because it is the only one that would not benefit from delocalization of the electron pair on the amide nitrogen.

Mechanism I

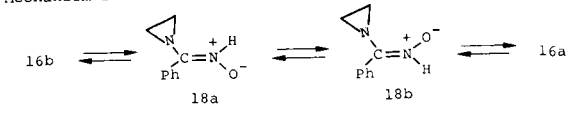


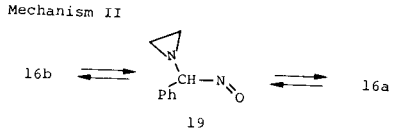
Table V

Some Amidoximes of Known Configuration

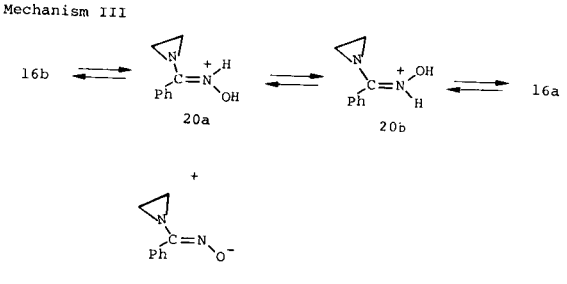
Compound number	Structure	Configuration of most stable isomer in solution	reference
8	Type C: R^1 and R^2 = $CH_2CH_2OCH_2CH_2$	*E*	7-9
9	Type D: R^1 and R^2 = $CH_2CH_2CH_2CH_2$; R^3 = CH_3	*E*	1
10	Type C: R^1 = C_6H_5; R^2 = CH_3	$Z \rightleftharpoons E$	8,9
11	Type A: R = H	*Z* [a]	12
12	Type A: R = CH_3 or $CH_2C_6H_5$	*Z*	13,14
13	Type B: R^1 = R^2 = CH_3	*Z* [b]	1
6	see text	*Z*	this work
14	Type A: R = C_6H_5	$Z \rightleftharpoons E$	15

[a] Only one isomer is known for benzamidoxime and its aromatic substituted derivatives. It is assumed that it is the most stable isomer. [b] Assumed to have the *Z* configuration.

Mechanism II



Mechanism III



EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Infrared spectra were determined with a Pye Unicam SP-1100 spectrometer. The mass spectrum was recorded at 70 eV on a CEC 21-104 mass spectrometer. The glc (analytical and preparative) were carried out with a column (30 ft. × 0.375 in.) consisting of either 20% Carbowax 100 M or 20% SE-30 on 45-60 mesh Chromosorb W. Ultraviolet irradiations were carried out in quartz test tubes placed in a merry-go-round apparatus in a Rayonet RPR-100 reactor (Southern New England Ultraviolet Company) fitted with RPR-2537Å lamps. Microanalyses were carried out at Atlantic Microlab, Atlanta, Georgia.

α-Methoxyphenylacetamidoxime (**3**).

A solution of sodium carbonate (48.8 g) in water (210 ml) was slowly added to an ice cold solution of hydroxylamine hydrochloride (32.7 g) in methanol (350 ml). The mixture was stirred for one hour and filtered. The filtrate was placed in a round bottomed flask and α-methoxyphenylacetonitrile [2,3] (64.6 g) was added slowly. The solution was refluxed for 24 hours, cooled to room temperature, and the methanol was evaporated at aspirator pressure. The solid which formed during evaporation of the methanol was collected by filtration and recrystallized from benzene to give colorless crystals (57.8 g, 90%), mp 128.5-129.5°; ir (Nujol): 3500, 3380, 1680 cm^{-1}, ^1H nmr (d_6-DMSO): δ 3.38 (s, 3, OCH_3), 4.37 (s, 1, CH), 5.33 (s, 2, NH_2), 7.30-7.61 (m, 5, aromatic H).

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.99; H, 6.71; N, 15.55. Found: C, 60.03; H, 6.75; N, 15.50.

O-Methyl-α-methoxyphenylacetamidoxime (**4**).

α-Methoxyphenylacetamidoxime (16.4 g) was suspended in a solution of sodium hydroxide (6.44 g) in water (1230 ml). The solution was gently heated with stirring until the amidoxime dissolved. Dimethyl sulfate (12.8 g) was then slowly added. After the addition was complete, heating was discontinued and the solution was stirred at room temperature for 4 hours. After storage in a refrigerator for 8 hours, the mixture was extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate and the ether was evaporated at aspirator pressure. The resulting residual oil crystallized on standing at room temperature. The crude product was recrystallized from water to give colorless crystals (10.9 g, 61%), mp 73-76°; ir (Nujol): 3480, 3320, 1650 cm^{-1}, ^1H nmr (deuteriochloroform): δ 3.41 (s, 3, $COCH_3$), 3.80 (s, 3, $NOCH_3$), 4.30-4.71 (br s, 2, NH_2), 4.68 (s, 1, CH), 7.26-7.54 (m, 5, aromatic).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.74; H, 7.30; N, 14.41.

O-Methyl-α-methoxyphenylacetohydroximoyl Chloride (**5**).

O-Methyl-α-methoxyphenylacetamidoxime (9.00 g) was dissolved in a solution of concentrated hydrochloric acid (12.0 ml) in water (200 ml) and cooled in an ice bath. A solution of sodium nitrite (4.50 g) in water (65 ml) was then added slowly. The mixture was stirred for 14 hours at room temperature and then extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated at aspirator pressure to give a yellow oil. Fractional distillation of the oil gave a light yellow oil (3.00 g, 31%), bp 125-133°/3.4 torr; ir (neat): 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.50 (s, 3, $COCH_3$), 4.08 (s, 3, $NOCH_3$), 5.10 (s, 1, CH), 7.31-7.68 (m, 5, aromatic H).

Anal. Calcd. for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 56.35; H, 5.72; N, 6.50; Cl, 16.44.

O-Methyl-α-ketophenylacetohydroximoyl Chloride (**1**).

O-Methyl-α-methoxyphenylacetohydroximoyl chloride (**5**, 2.00 g) and *N*-bromosuccinimide (2.10 g) were placed in a round bottomed flask containing carbon tetrachloride (50 ml). Hydrobromic acid (0.85 ml of 48%)

was added, the flask was fitted with a reflux condenser protected by a calcium chloride drying tube, and the mixture was refluxed for 30 hours. The mixture was cooled to room temperature, the carbon tetrachloride was evaporated to a small volume, and the mixture was filtered. The filter pad was washed with carbon tetrachloride (200 ml), the filtrate was dried over anhydrous magnesium sulfate, and the carbon tetrachloride was removed by evaporation at aspirator pressure. The residual oil (2.20 g) was analyzed by glc and found to contain **5** (5%) and **1** (95%). The hydroximoyl chloride **1** was separated from the mixture by preparative glc (SE-30). Microdistillation at reduced pressure of the glc effluent gave **1** as a colorless oil; ir (neat): 1680, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 4.17 (s, 3, CH_3), 7.55-8.10 (m, 5, aromatic H); ms: m/z (relative intensity) 199 (1.12), 197 (3.39), 131 (5.91), 105 (100), 77 (69.7).

Anal. Calcd. for $C_9H_8ClNO_2$: C, 54.70; H, 4.08; N, 7.09; Cl, 17.94. Found: C, 54.77; H, 4.09; N, 7.07; Cl, 17.89.

3-Phenyl-5,6-dihydro-2(1*H*)-pyrazinone-*O*-methyloxime (**6**).

Ethylenediamine (1.22 g) was slowly added with stirring to a solution of *O*-methyl-α-ketophenylacetohydroximoyl chloride (**1**, 1.00 g) in benzene (30 ml) and the resulting solution was refluxed for 3 hours. After cooling to room temperature, dilute aqueous sodium hydroxide was added to the solution until the mixture was basic to litmus. The benzene was removed by evaporation at aspirator pressure and the aqueous solution was extracted with methylene chloride. The methylene chloride extracts were dried over magnesium sulfate and the methylene chloride was evaporated at aspirator pressure to give a light yellow solid. Recrystallization of the solid from a methanol-water solution gave colorless crystals of **6** (0.40 g, 39%), mp 92.5-94.5°; ir (Nujol): 3300, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.30 (m, 2, $NHCH_2$), 3.85-4.10 (singlet at δ 3.90 superimposed on a multiplet, 5, OCH_3 and $=NCH_2$), 5.45 (broad s, 1, NH), 7.30-7.60 (m, 3, aromatic H), 7.70-8.04 (m, 2, aromatic H).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 65.14; H, 6.50; N, 20.62.

3-Phenyl-5,6-cyclohexano-5,6-dihydro-2(1*H*)-pyrazinone-*O*-methyloxime (**7**).

1,2-*trans*-Diaminocyclohexane (4.56 g) was slowly added with stirring to a solution of *O*-methyl-α-ketophenylacetohydroximoyl chloride (**1**, 2.00 g) in benzene (75 ml) and the resulting solution was refluxed for 12 hours. After cooling to room temperature, water (20 ml) was added, and the mixture was extracted with ether (2 × 15 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated at aspirator pressure. The residual viscous brown oil was chromatographed through silica gel using chloroform-hexane (30:70) as the eluant. The tan crystals (1.50, 61%, mp 79.5-82°) obtained from column chromatography were recrystallized from a chloroform-hexane solution to give tan crystals of **7**, m.p. 80-83°; ir (thin film prepared by evaporation of a benzene solution of **7** on a sodium chloride disk): 1580, 1600, 1625, 3440 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.10-2.60 (m, 8, $(CH_2)_4$), 2.65-3.32 (m, 2, CHCH), 3.88 (s, 3, CH_3), 7.25-7.57 (m, 3, aromatic H), 7.68-8.00 (m, 2, aromatic H).

Anal. Calcd. for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.08; H, 7.48; N, 16.33.

(*Z*)-Aziridinylbenzaldoxime (**16a**) [22,23].

A solution of benzohydroximoyl chloride [24] (20.0 g) in dry ether (150 ml) was added to an ice cold solution of aziridine (11.1 g) and triethylamine (9.74 g) in dry ether (50 ml). The resulting solution was stirred for one-half hour at 0°C. Water (100 ml) was added to the solution, and the mixture was extracted several times with ether. The combined ether extracts were dried over anhydrous magnesium sulfate, and the ether was evaporated to give a colorless solid. Recrystallization from ether-hexane gave colorless crystals (10.1 g, 87%), mp 120-121°; ir (Nujol): 3300, 1600, 1584 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.32 (s, 4, CH_2CH_2), 7.26-7.57 (m, 3, aromatic H), 7.68-7.97 (m, 2, aromatic H).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.64; H, 6.34; N, 17.32.

Photoisomerization of (*Z*)-Aziridinylbenzaldoxime (**16a**).

Ultraviolet irradiation of a 0.1 *M* solution of (*Z*)-aziridinylbenzaldoxime (**16a**) in benzene for 3 hours gave a mixture of two isomers as indicated by the ^1H nmr spectrum of the photolysis product. The ^1H nmr spectrum (deuteriochloroform) of the mixture showed two aziridinyl methylene singlets at δ 2.30 (**16a**) and δ 2.14 (**16b**).

(*Z*)-*O*-Methylaziridinylbenzaldoxime (**17a**).

Dimethyl sulfate (12.5 g) was added dropwise to a cold, stirred solution of aziridinylbenzaldoxime (**16a**, 15.3 g) in 0.7 *N* sodium hydroxide solution (153 ml). The mixture was kept in an ice cold bath for four hours after the addition was complete. The reaction mixture was then extracted with ether (50 ml × 4) and the combined ether extracts were dried over anhydrous magnesium sulfate. The ether was evaporated at aspirator pressure to give an oil which crystallized on cooling. Recrystallization of the crude product from ether-petroleum ether (bp 30-60°) produced **17a** as colorless crystals (9.17 g, 55%), mp 35-36°; ir (Nujol): 1554, 1586, 1591 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.22 (s, 4, CH_2CH_2), δ 3.95 (s, 3, OCH_3), 7.25-7.90 (two multiplets, 3 and 2, aromatic H).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.05; H, 6.91; N, 15.87.

(*E*)-*O*-Methylaziridinylbenzaldoxime (**17b**).

Ultraviolet irradiation of a 0.1 *M* solution of **17a** in benzene for 3 hours gave a mixture of the *Z* and *E* isomers as indicated by the ^1H nmr spectrum of the oil obtained by evaporation of the benzene. Separation of the mixture of isomers by preparative glc (Carbowax 100 M) gave (*E*)-*O*-methylaziridinylbenzaldoxime (**17b**) as a colorless oil; ir (neat): 1532, 1585, 1610, ^1H nmr (deuteriochloroform): δ 2.08 (s, 4, CH_2CH_2), δ 3.80 (s, 3, OCH_3), 7.25-7.55 (m, 3, aromatic H), 7.60-7.92 (m, 2, aromatic H).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.29; H, 6.92; N, 15.78.

(*Z*)-*O*-Methylpiperidinylbenzaldoxime (**21a**).

A solution of (*Z*-*O*-methylbenzohydroximoyl chloride [1] (0.75 g) in freshly distilled piperidine (17.0 g) was stirred at room temperature for 5 days in the dark. Ether (50 ml) was added and the piperidine hydrochloride which had formed during the reaction was removed by suction filtration. The piperidine hydrochloride in the funnel was washed with ether (10 ml). The filtrate was placed in a separatory funnel and washed with water (3 × 5 ml). The ether was dried over magnesium sulfate and evaporated at aspirator pressure (room temperature). The residual oil was then kept in a vacuum (< 0.5 torr) at room temperature for 24 hours. Since the ^1H-nmr spectrum of the residue showed that a trace of piperidine was contaminating the product, the oil was redissolved in ether (50 ml) and washed with water (2 × 25 ml). After removing the ether and drying the oil at room temperature in a vacuum (< 0.5 torr), a light yellow oil (0.76 g, 79%) was obtained; ir (neat): 1578, 1602 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.61 (broad singlet, 6, $CH_2CH_2CH_2CH_2CH_2$), 3.29 (m, 4, CH_2NCH_2), 3.87 (s, 3, OCH_3), 7.32-7.72 (m, 5, aromatic H).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.40; H, 8.32; N, 12.74.

Thermal Isomerization of (*Z*)-*o*-Methylpiperidinylbenzaldoxime (**21a**).

When *Z*-*O*-methylpiperidinylbenzaldoxime (**21a**) was passed through a glc column (SE-30, 190° and a flow rate of 40 ml/min) it underwent isomerization to give a mixture of the *Z* and *E* isomers (**21a**:**21b** = 10:90 from ^1H nmr). The isomerization also could be accomplished by heating a solution (d_6-DMSO or deuteriochloroform) of **21a** in a sealed, degassed nmr spin tube for 5 days at 100°. The equilibrium distribution of **21a** and **21b** obtained by thermal isomerization in solution was 10:90 as determined by integration of the OCH_3 singlets in the ^1H nmr spectrum of the mixture. The analytical sample of **21b** (containing 10% of **21a**) was obtained by preparative glc; ir (neat): 1577, 1589, 1685 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.55 (broad, 6, $CH_2CH_2CH_2CH_2CH_2$), 3.04 (m, 4, CH_2NCH_2), 3.68 and 3.87 (two singlets, the larger singlet at 3.68 for the

OCH_3 of **21b** and the smaller singlet at 3.87 for the OCH_3 of **21a**, the ratio of the singlets at 3.68 and 3.87 is 90:10, integrating for a total of 3H), 7.41 (s, 5, aromatic H).

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.59; H, 8.35; N, 12.88.

Kinetic Method.

A recrystallized (ether-hexane) mixture of **16a** and **16b** was dissolved in deuteriochloroform in a nmr spin tube and degassed on a vacuum line at $< 10^{-3}$ torr by the freeze-thaw method. After three freeze-thaw cycles, the tube was sealed and suspended in a constant-temperature bath at 100.0° (± 0.1°). C) The nmr tube was removed from the bath at various time intervals and the ^1H nmr spectrum was determined in the region of the aziridinyl methylene absorptions. The rate of the isomerization of **16a** to **16b** was determined from integration of the methylene singlets. The isomerization of (*Z*)-*O*-methylpiperidinylbenzaldoxime (**18a**) to the *E* isomer (**18b**) was followed by integration of the methoxy singlets of the two isomers.

Structure Determination of **6**.

Unit-cell parameters were obtained by least-squares fit of 15 reflections in the range $20 < 2\theta < 30°$ measured on a Syntex P2, diffractometer. The crystal data are summarized in Table 1. The intensity data were collected in the $\theta/2\theta$ scan mode using graphite monochromated MoK radiation. Three standard reflections remeasured at intervals of every 100 reflections did not show any significant change during data collection. The intensity data were corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by direct methods using MULTAN78 [25] which showed the positions of all non-hydrogen atoms. Refinements were carried out using SHELX76 [26]. The positions of all hydrogen atoms were located on successive difference Fourier maps. All non-hydrogen atoms were refined anisotropically, all hydrogen atoms isotropically. In the final stages of refinement, a weighting scheme $w = 1/(\sigma_F^2 + 0.002140F^2)$ was applied. The quantity minimized in the least-squares was $\Sigma w (|F_o| - |F_c|)^2$. Two reflections, 0 4 3 and 1 2 4, possibly affected by extinction were taken out during the last refinement. The final agreement factors are $R = 0.038$ and $R_w = 0.042$ for 1652 observed reflections. The maximum shift in the final cycle of refinement was 0.14σ. The atomic scattering factors for C, H, N and O used were those stored in SHELX76. The final atomic coordinates and temperature factors are given in Table 2. Bond lengths and bond angles are listed in Table 3 and some selected torsion angles are presented in Table 4.

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