Novel Reactions of Ketoximes with Nitrosyl Chloride[1]

CHYNG-YANN SHIUE, KYONG PAE PARK, AND LEALLYN B. CLAPP

Metcalf Chemical Laboratories, Brown University, Providence, Rhode Island 02912

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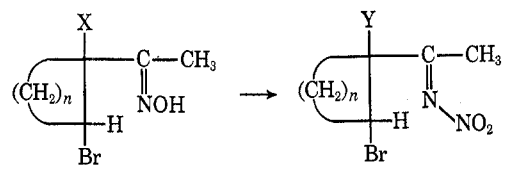
Rheinboldt[2] discovered that nitrosyl chloride[3] would react with aldoximes to give chloronitroso compounds, RCHClNO, or hydroxamic chlorides, ArCCl=NOH, or with ketoximes to give *gem*-chloronitroso compounds. Nitrosyl chloride has been used much more extensively to add to olefins to give β-chloronitroso compounds[3] (normal addition) or in some cases dichloro, chloronitro, or dichloronitroso (anomalous) products.[3a,4] If the β-chloronitroso compound has an α hydrogen, it isomerizes more or less readily to a chloro ketoxime.

We have found a quite different result when compounds of type I are treated with nitrosyl chloride. Two reactions occur. The oximino group is oxidized to



Ia, $n = 3$; X = OCH_3
b, $n = 3$; X = Br
c, $n = 4$; X = OCH_3
d, $n = 4$; X = Br
e, $n = 5$; X = OCH_3
f, $n = 5$; X = Br
g, $n = 4$; X = Br, t-C_4H_9 on C_4

IIa, $n = 3$; Y = OCH_3
b, $n = 3$; Y = Cl
c, $n = 4$; Y = OCH_3
d, $n = 4$; Y = Cl
e, $n = 5$; Y = OCH_3
f, $n = 5$; Y = Cl
g, $n = 4$; Y = Cl

a nitrimine II, a result that has been accomplished by nitrous acid oxidation[5] and by nitrosyl fluoride[6] but not by nitrosyl chloride. In the case of α-bromo ketoximes Ib, d, f, and g, the oxidation is preceded by replacement of bromine with chlorine to give IIb, d, f, and g. The oxidizing action of nitrosyl chloride has been established,[7,8] but the replacement reaction is new.

The mechanism of nitrimine formation (new N–N bond formation at the oximino nitrogen by an electrophilic NO^+ group, followed by an oxygen shift) suggested by Freeman[5,9] and supported by Boswell[6] seems adequate to account for the present results.

Acetylcycloalkenes were synthesized by a Friedel–Crafts reaction[10,11] and converted into unsaturated ketoximes by a standard method. Bromine addition to the oxime gave compounds Ib, d, f, and g. The stereochemistry of the oximes is unspecified in compounds I. Reaction of the dibromo compound with methanol easily replaced the tertiary bromine[12] to give Ia, c, and e. All of the compounds I then gave compounds II with nitrosyl chloride.

The sharp OH absorption at 3600 cm^{-1} characteristic of oximes[13] in *dilute* carbon tetrachloride solution disappears as the reaction occurs. Each of the compounds II show strong bands at 1580 and 1320 cm^{-1} (NO_2) and medium bands at 1640 cm^{-1} (C=N), characteristic of nitrimines.[5,14] The ultraviolet spectrum of each compound gave a low intensity absorption (ϵ_{max} ~600) at 263–270 mμ[5] in 95% ethanol. The methyl protons in IIa, c, and e gave a chemical shift of δ ~2.03 and those in IIb, d, f, and g gave a shift of δ ~2.2.

The identity of the nitrimine structure was further verified by the reduction of IIa to be corresponding nitramine with lithium aluminum hydride.[5] The halogen was untouched by the strong basic reagent. Compounds IIa and c were hydrolyzed in sulfuric acid solution to the corresponding α-bromo ketones.[15]

Sodium iodide in acetone replaces the α-bromine in Ib, d, and f which is followed by loss of halogen to give 1-acetyl-1-cycloalkene oxime. In contrast, compound IId does not react with sodium iodide in acetone nor is chlorine or bromine displaced by alcoholic silver nitrate solution. The bromine in Id reacts rapidly with ethanolic silver nitrate. Compound IId is also recovered unchanged after 12-hr reflux with 30% sulfuric acid in contrast to the easy hydrolysis of other nitrimines.[16] The remarkable stability of chlorobromo compound IId and the lability of the α-bromine in Id certainly suggests that bromine displacement in Id occurs before oxidation to nitrimine.

Experimental Section

1-Acetylcyclopentene.—1-Acetylcyclopentene was prepared by the method of Casals[17] in 77% yield. The compound was identified by its 2,4-dinitrophenylhydrazone derivative, mp 201–203°[17] and ir spectrum. The oxime was prepared (yield 41%) by a well-known procedure[18] and sublimed at low pressure for the analytical sample.

Other acetylcycloalkenes were prepared by a Friedel–Crafts procedure[11] and their oximes by a standard method.[18]

The acetylcycloalkenes showed the following absorption in the ir spectra (cm^{-1}, dilute CCl_4): vinyl CH, 3050–3075 (s); C=O, 1720 (s), 1670–1675 (s); C=C, 1640–1650 (w). The nmr spectrum of 1-acetyl-1-cyclopentene follows (CCl_4): δ 6.68 (s, 1), 2.25 (s, 3), 1.8–2.7 (m, 6). The nmr spectra of other acetylcycloalkenes were consistent with these chemical shifts for vinyl CH, acetyl CH_3 groups, and methylene groups.

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TABLE I

PROPERTIES OF METHYL CYCLOALKYL KETOXIMES

1-Acetyl derivative	Yield, %	Oxime Mp, °C	Oxime Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Cyclopentene	77	94–95.5	41	67.17	8.86	11.19	67.32	8.74	10.94
Cyclohexene	73	63.0–63.5	73	69.03	9.41	10.07	69.30	9.57	10.21
Cycloheptene	56	59–60	62	70.49	9.87	9.13	70.70	9.69	9.10
4-*t*-Butylcyclohexene		156–157	38	73.78	10.85	7.17	73.80	10.79	7.13

TABLE II

PROPERTIES OF COMPOUNDS I AND II

Compd	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Br	Found, % C	Found, % H	Found, % N	Found, % Br
Ia	37	106–107	40.69	5.98	5.93		40.65	6.27	5.93	
Ib	77	77–78	29.49	3.89	4.92		29.33	4.08	4.96	
IIa		69–70	36.23	4.95	10.57		36.50	5.20	10.40	
IIb		57–58	31.20	3.76	10.42		31.43	3.76	10.54	
Ic	90	133–134.5	43.23	6.41	5.60	31.96	43.45	6.46	5.53	32.09
Id	100	118–119	32.15	4.38	4.68	53.46	32.41	4.49	4.78	53.57
IIc	89	71–73	38.73	5.41	10.03		38.78	5.62	10.07	
IId	40	57–58	33.87	4.61	9.87		33.65	4.26	9.62	
Ie	30	130.5–132	45.45	6.87	5.32		45.47	6.77	5.24	
If	44	100–101	34.52	4.83	4.47		34.94	4.79	4.59	
IIe		Oil								
IIf	15	60.5–62	36.31	4.74	9.41		36.47	4.74	9.31	
Ig	20	134–135.5	40.56	5.96	3.94		40.54	5.68	3.67	
IIg	40	92–93	42.41	5.94	8.24		42.53	5.79	8.22	

The corresponding oximes gave the following absorptions in the ir spectra (cm^{-1}, dilute CCl_4): oxime OH, 3590 or 3610 (s); H bond, 3200–3300; C=N, C=C, 1630–1650. Nmr spectrum of 1-acetyl-1-cyclopentene oxime (CCl_4): δ 9.8 (s, 1, NOH), 6.01 (m, 1), 2.0 (s, 3), 1.8–2.8 (m, 6). Other oximes had consistent nmr patterns. See Table I for analyses.

Methyl 1,2-Dibromo-1-cyclopentyl Ketoxime (Ib).—Addition of bromine in carbon tetrachloride to the corresponding ketoxime gave the dibromo derivative in 77% yield. The solvent was removed and the oxime was recrystallized from a carbon tetrachloride–pentane mixture, mp 77–78.5°. The compound decomposed when exposed to light and was kept in a sealed container.

Other dibromo compounds were obtained in quantitative yields by the same method. When the corresponding dibromo ketones were oximated, low yields or no yields of dibromo ketoximes were obtained and the compound lost hydrogen bromide continuously.[19] The dibromo oximes gave the following ir absorption bands (cm^{-1}, dilute CCl_4): oxime OH, 3580–3600 (s); C=N, 1650–1670 (w). The nmr spectrum of Ib follows (CCl_4): δ 4.7 (d, 1, CHBr), 2.1 (s, 3), 1.9–3.0 (m, 6). The nmr spectra of the other dibromo compounds, Id, f, and g are consistent with the spectra of Ib.

Sodium iodide (75 mg, 0.5 mmol) was dissolved in 10 ml of acetone and shaken with 36 mg (0.12 mmol) of Id. Sodium bromide precipitated at once, but the mixture was allowed to stand overnight. The white precipitate was filtered and acetone was removed on a rotatory evaporator. The remaining oil was taken up in water and extracted with carbon tetrachloride. Evaporation of the carbon tetrachloride gave 12 mg (70%) of a solid, identified as 1-acetylcyclohexene oxime by comparison with the nmr spectrum of an authentic sample (CCl_4): δ 1.97 (s, 3), 6.12 (m, 1).

In contrast, IId was recovered unchanged after refluxing with sodium iodide in acetone for 2.5 hr and standing overnight.

Methyl 1-Methoxy-2-bromo-1-cyclopentyl Ketoxime (Ia).—Compound Ib (2 g, 7.0 mmol) (above) was dissolved in 30 ml of absolute methanol and stirred for 20 hr at ambient temperatures. The solution was poured into ice and the precipitate was collected and dried, yield 0.61 g (37%), mp 104–106°. The analytical sample was recrystallized twice from aqueous methanol, mp 106–107°.

The yield was not improved by adding anhydrous sodium carbonate to the reaction mixture. Other bromomethoxy ketoximes were prepared in similar fashion. Addition of N-bromosuccimmide in methanol to 1-acetyl-1-cyclohexene gave the corresponding bromomethoxy ketone, but we were unable to convert this compound into the oxime, Ic.

Ir spectra of the bromomethoxy ketoximes were taken in dilute carbon tetrachloride solution: NOH, 3590–3600 (s); C=N, 1650 (w); C—O, 1060–1090. Nmr spectrum of Ia follows (CCl_4): δ 4.15 (d, 1, CHBr), 3.1 (s, 3, OCH_3), 1.9 (s, 3, CH_3). In compound Ic, the oximino proton was shifted to δ 10.00 (s) while it was smeared out and not identified in the other bromomethoxy compounds. The CHBr proton appeared at a consistent point.

Methyl 1-Methoxy-2-bromocyclohexyl Nitroketimine (IIc).—Compound Ic (2 g, 8 mmol) was dissolved in 30 ml of carbon tetrachloride at room temperature and a slow stream of nitrosyl chloride gas was bubbled through it. After the solution became dark brown the gas stream was stopped and the solution was allowed to stand for 10 min. Then 2 g of anhydrous sodium carbonate was added and the mixture was allowed to stand for 1 hr. Solids were removed from the green oil by filtration and the solvent was removed on a rotating evaporator. The green oil solidified in the refrigerator, yield 2.0 g (89%), mp 65–66°. Three recrystallizations from pentane and two sublimations gave the analytical sample, mp 71–73°.

Other nitrimines (II) were prepared by a similar procedure. Ir spectra of the nitrimines II were taken in dilute carbon tetrachloride solution: C=N, 1630–1640; NO_2, 1580 and 1320. Nmr spectrum of IIc follows (CCl_4): δ 4.22 (br, 1, CHBr), 3.23 (s, 3, OCH_3), 2.03 (s, 3, CH_3). Other compounds II had spectra consistent with these chemical shifts.

Compound IIc (50 mg) was dissolved in 20 ml of carbon tetrachloride and 1 ml of sulfuric acid was added. The mixture was stirred at room temperature for 1.5 hr. The reaction mixture was neutralized with cold aqueous potassium hydroxide solution and the aqueous layer was extracted with carbon tetrachloride. The solvent was dried with anhydrous magnesium sulfate and then the carbon tetrachloride was removed. One drop of oil remained which had the following properties: ir (cm^{-1}, CCl_4) C=O, 1720 (s); nmr (CCl_4) δ 4.3 (br, 1), 1.5~2.5 (m, 8). The spectrum was identical with that of an authentic sample of α-bromocyclohexanone.[15]

Other properties of compounds I and II appear in Table II.

Reduction of the Nitrimine IIa to a Nitramine.—A solution of 1.38 g (5.2 mmol) of compound IIa in 50 ml of dry ether was added to a slurry of 0.5 g of lithium aluminum hydride[5] in 100 ml of dry ether. The reaction mixture was stirred overnight at ambient temperatures and then refluxed for 24 hr. The mixture was poured into 500 ml of ice water and neutralized with dilute

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HCl. A yellow solid was extracted with ether and dried, yield 1.05 g (76%). Recrystallization from pentane and sublimation at low pressure gave the analytical sample of 1-α-nitraminoethyl-1-methoxy-2-bromocyclopentane, mp 105–106°, 112° dec.

Anal. Calcd for $C_8H_{15}N_2O_3Br$: C, 35.95; H, 5.66; N, 10.49. Found: C, 36.31; H, 5.72; N, 10.60.

The ir spectrum of the nitramine was taken in dilute carbon tetrachloride (cm^{-1}): NH, 3360; NO_2, 1580 and 1340. The nmr spectrum (CCl_4) follows: δ 4.83 (q, 1, J = 7 Hz), 4.17 (br, 1), 3.4 (s, 3), 1.33 (d, 3, J = 7 Hz). The uv spectrum was taken in 95% ethanol: λ_{max} 232 mμ (ε 8500).[5,20]

Registry No.—Ia, 23042-83-3; Ib, 23042-84-4; Ic, 23042-85-5; Id, 23042-86-6; Ie, 23042-87-7; If, 23042-88-8; Ig, 23042-89-9; IIa, 23042-90-2; IIb, 23042-91-3; IIc, 23042-92-4; IId, 23042-93-5; IIe, 23042-94-6; IIf, 23042-95-7; IIg, 23042-96-8; 1-acetylcyclopentene oxime, 23042-97-9; 1-acetylcyclohexene oxime, 23042-98-0; 1-acetylcycloheptene oxime, 23042-99-1; 1-acetyl-4-*t*-butylcyclohexene oxime, 23043-00-7; 1-α-nitraminoethyl-1-methoxy-2-bromocyclopentane, 23043-01-8.

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Fused-Ring Isoxazolines and Their Isomers[1]

KYONG PAE PARK, CHYNG-YANN SHIUE, AND LEALLYN B. CLAPP

Metcalf Chemical Laboratories, Brown University, Providence, Rhode Island 02912

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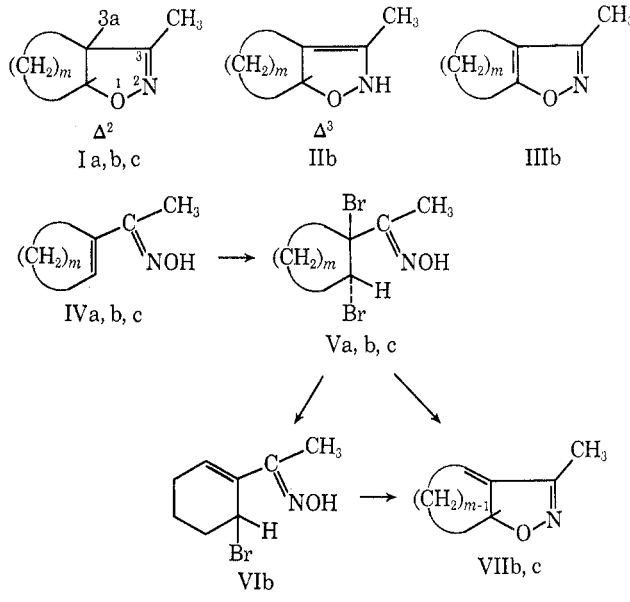
Δ²-Isoxazolines[2] are commonly synthesized from α,β-unsaturated carbonyl compounds by treatment with hydroxylamine. The extensive work of Barnes,[2] Blatt,[2] and von Auwers[2] has shown that the isoxazolines do not arise by direct cyclization (Michael self-addition) of the unsaturated oxime. No Δ³-isoxazoline with an unsubstituted NH[3] has been reported, but a Δ⁴-isoxazoline has recently been postulated as an intermediate in the pathway to an aziridine.[4,5]

We have synthesized a series of Δ²-isoxazolines I, the unsaturated isomeric oximes IV, and the unsaturated isomeric fused ring compounds III and VII. The cycloalkene added the elements of acetonitrile oxide[6,7] to give the Δ²-isoxazolines I. These isoxazolines do not add bromine at room temperature in a period of 24 hr. By oxidation with N-bromosuccinimide[8] Ib was converted in 67% yield to IIIb. The isoxazoline Ib was not oxidized to IIIb by chromic acid in acetic acid,[9] the usual reagent for converting the isoxazoline to an isoxazole. Compounds Ia and Ic gave 3a-bromo derivatives by action of N-bromosuccinimide, but IIIa was not formed by dehydrobromination, and IIIc was too unstable to isolate for analysis. Compound IIIc was identified by ir and nmr spectra (Table I).



Condensation of the 1-acetylcycloalkenes with hydroxylamine in the presence of pyridine gave the unsaturated oximes IV, isomers of I. Compounds IV added bromine (accepted as a *trans* addition) to give *trans*-dibromo derivatives V. The small dipole moment of Vb (0.59 D in benzene) is compatible with the *trans* structure. Acetone oxime, for example, has a dipole moment of 0.88 D.[10] *trans* elimination of HBr to give VIIb is also consistent with the proposed stereochemistry of Vb. Dehydrobromination of Vb with 1 mol of triethylamine in homogeneous medium yielded VIb, identified by nmr spectra and isolated as a glass. Compounds VIIb,c were obtained in a two-phase reaction by shaking solutions of Vb,c in carbon tetrachloride over sodium hydroxide pellets. Compound VIb was also converted to VIIb by the same method. However, compound Va did not undergo the dehydrobromination reactions carried out in a similar way. The allylic bromide VIb is a logical reactive precursor of VIIb. The nonreactivity of Va by comparison with Vb toward dehydrobromination is explained by Brown's I-strain theory.[11] A five-membered ring reluctantly forms an *endo* double bond which would be the case if VIa were a precursor to VIIa. On the other hand, a six-membered ring readily forms an *endo* double bond[11] (VIb) in the pathway to VIIb. Presumably the seven-membered-ring VIc would be subject to internal strain more closely resembling that of the six-membered ring than the five-membered ring. Compound VIc was not isolated but VIIc was isolated and identified.

(1) Support by Public Health Service Grant CA-07521 is gratefully acknowledged. The Varian A-60A nmr spectrometer and the mass spectrometer used in this research were purchased under a National Science Foundation Research Instrument Grant.

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