Table I. Oxidation of Phenacyl Bromides with *N,N*-Dialkylhydroxylamine[a]

$ArCOCH_2Br$ (I), Ar	Registry no.	ArCOCHO (yield, %)[b]	Registry no.	Mp of hydrate (lit. mp), °C
Ph	70-11-1	78 (80)[c]	1074-12-0	90–91 (90)[d]
p-BrPh	99-73-0	68 (74)[c]	5195-29-9	119–122 (128–129)[e]
p-PhPh	135-73-9	90 (75)[c]	4974-58-7	113–117 (117–121)[f]
m-MeOPh	5000-65-7	55	32025-65-3	99–100 (98–101)[g]
β-Naphthyl[h]	613-54-7	76	22115-06-6	93–96 (98)[d]

[a] All reactions were carried out in methanol at reflux for 2 h, except as otherwise noted. [b] As the glyoxal hydrates. [c] Yields with *N,N*-dibenzylhydroxylamine, *without* distillation. [d] "Heilbron's Dictionary of Organic Compounds". [e] G. A. Russel and G. J. Mikol, *J. Am. Chem. Soc.*, **88**, 5498 (1966). [f] F. Krohnke and E. Borner, *Ber.*, **69B**, 2006 (1936). [g] R. B. Moffett, B. T. Tiffany, B. D. Aspergren, and R. V. Heinzelman, *J. Am. Chem. Soc.*, **79**, 1687 (1957). [h] Reaction time: 8 h.

zine, one can postulate the initial formation of 1,1-diethyl-1-phenacylhydroxylammonium bromides (**5**)[2,4a] followed by a Meisenheimer rearrangement[6] of the amine *N*-oxides (**6**) to the *O*-phenacylhydroxylamines (**7**).[7] These latter intermediates could then fragment to the arylglyoxals and diethylamine, which was isolated as its hydrobromide salt in each case in nearly quantitative yields. Extension of this oxidation to other α-halo carbonyls has so far been less successful. Although benzil was obtained from the reaction of desyl chloride and DEHO, albeit in only 25% yield, so far only complex products and recovered starting materials have been obtained with 2-chlorocyclohexanone and α-bromopropiophenone. In the case of benzil, a control experiment clearly indicated that *N,N*-diethylhydroxylamine reacted further with benzil to give less than 30% of recovered benzil; no definite product has yet been isolated from the dark residue of this reaction.[8]

The Cope elimination is a competitive reaction when β hydrogens are available in the amine *N*-oxides.[6,9] In order to investigate this possibility, the reaction of phenacyl bromide with *N,N*-dibenzylhydroxylamine[10] was carried out. The reaction proceeded much more slowly (an orangy color develops almost immediately after mixing phenacyl bromide with DEHO) and a longer reflux period had to be used for the reactions to take place. Although the yields of arylglyoxals were not substantially different (see Table I), the undistilled products in these cases were nearly as pure as those obtained with DEHO *after* the distillation. This suggests that the Cope elimination, though not a major problem, may be occurring to a small extent, thus explaining the lesser purity of the products obtained with DEHO.

Thus, the reaction of *N,N*-diethylhydroxylamine with phenacyl bromide offers a useful and mild "nonoxidative" route to arylglyoxals. We are at present investigating the scope and mechanism of this reaction, with particular attention to the possible intervention of radicals in the putative Meisenheimer rearrangement.

Experimental Section

All melting points are uncorrected. *N,N*-Diethylhydroxylamine was obtained from Pennwalt Corp. and was distilled prior to use. *N,N*-Dibenzylhydroxylamine was prepared according to a published procedure.[10] The phenacyl bromides were used as purchased or prepared according to literature directions.

Oxidation of Phenacyl Bromides with *N,N*-Dialkylhydroxylamines. A. With *N,N*-Diethylhydroxylamine. A solution of 8.56 g (0.043 mol) of phenacyl bromide and 3.83 g (0.043 mol) of *N,N*-diethylhydroxylamine in 80 ml of methanol was heated to reflux with stirring for 2 h. Evaporation of the solvent followed by addition of 75 ml of ether to the residue precipitated diethylamine hydrobromide, mp 203–206 °C dec (lit.[11] mp 205 °C), in nearly quantitative yield. Evaporation of the ethereal solution left a residue which was distilled in vacuo to yield 4.5 g (78%) of phenylglyoxal. The other glyoxals reported in Table I were obtained by the same procedure.

B. With *N,N*-Dibenzylhydroxylamine. A solution of 5.00 g (0.025 mol) of phenacyl bromide and 5.33 g (0.025 mol) of *N,N*-dibenzylhydroxylamine in 80 ml of methanol was heated to reflux with stirring for 48 h. Evaporation of the solvent followed by addition of 80 ml of ether to the residue precipitated 5.31 g (76%) of dibenzylamine hydrobromide, mp 262–265 °C (lit.[12] mp 266 °C). Evaporation of the ethereal solution left a residue whose infrared spectrum matched that of the distilled compound above. The other glyoxals reported in Table I were obtained by the same procedure.

Acknowledgment. It is a pleasure to acknowledge generous gifts of *N,N*-diethylhydroxylamine from Mr. L. Gilette of the Pennwalt Co., Philadelphia, Pa.

Registry No.—*N,N*-Diethylhydroxylamine, 3710-84-7; *N,N*-dibenzylhydroxylamine, 621-07-8; dibenzylamine hydrobromide, 103-49-1.

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Heterocyclic Derivatives Formed from 2-Alkoxyimino Aldehydes and 1,2-Disubstituted Ethanes

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The preparation of 2-alkoxyimino aldehydes, **1**, by selenium dioxide oxidation of alkoxyiminoalkanes[1] provided a functional group adjacent to an oxime which was susceptible to derivatization by nucleophilic reagents.[2] Derivatization of the aldehyde moiety with molecules containing two nucleophilic

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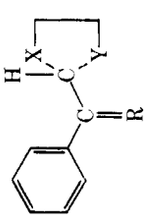
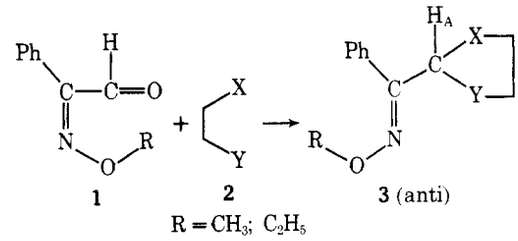
Table I. Compounds Prepared by Reaction of 1,2-Substituted Ethanes with 2-Alkoxyimino Aldehydes



Registry no.	R	X	Y	Bp, °C (Torr)	Refractive index	Mp, °C	Yield, %	Composition	Calcd, %				Found, %			
									C	H	N	S	C	H	N	S
53056-09-0		O	O			81–82	52	$C_{11}H_{13}NO_3$	63.77	6.28	6.76		63.63	6.45	6.56	
60978-34-9		O	O			51–52	45	$C_{12}H_{15}NO_3$	65.16	6.79	6.33		65.04	6.95	6.33	
60978-35-0		O	S	118–123 (0.008)	n^{23} 1.5587		12	$C_{11}H_{13}NO_2S$	59.19	5.83	6.28	14.35	59.08	5.62	6.35	14.40
60978-36-1		O	S	112–113 (0.008)	n^{23} 1.5571		39	$C_{12}H_{15}NO_2S$	60.76	6.33	5.91	13.50	60.55	6.29	5.98	13.61
21504-27-8		S	S			113–114	76.8	$C_{12}H_{14}S_4$	50.21	5.01		44.70	50.15	5.06		44.50

Scheme I



1 2 3 (anti)

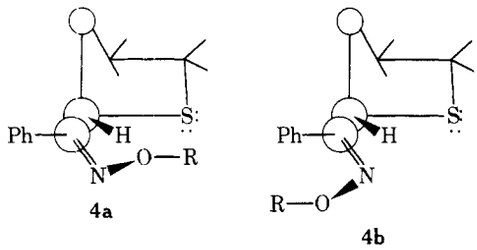
R = CH_3; C_2H_5

sites was carried out to generate heterocyclic systems (Scheme I), adjacent to the oxime function. Reaction of 1 with ethylene glycol (**2**, X = Y = O) and 2-mercaptoethanol (**2**, X = O; Y = S) proceeded to yield the corresponding cyclic acetal (**3**, X = Y = O) and hemithioacetal (**3**, X = O; Y = S), respectively. Starting with a pure geometric isomer of the aldehyde, **1**, the 1,3-dioxolane (**3**, X = Y = O) was synthesized without change in the configuration about the imino double bond. The oxathiolane, formed by reaction with mercaptoethanol (using either BF_3 or *p*-toluenesulfonic acid as catalyst), was a mixture of geometric isomers formed by apparent isomerization of the oxime group as determined by examination of the ^1H NMR spectra of the derivative. The methine proton, H_A, in compound **3** (X = O; Y = S; R = C_2H_5) appears as two single lines at 6.38 and 5.92 ppm, the upfield signal being 2.5 times greater in area than the downfield signal.[3] In addition, the methyl protons (1.2 ppm) appear as a complex multiplet, indicating a mixture of products, although only integrating for three protons.

When the spectrum of **3** (X = O; Y = S; R = C_2H_5) was determined in deuteriochloroform or tetrahydrofuran at or above 60 °C, the relative line intensities of the methine ring proton, H_A, changed irreversibly, so that the downfield peak was 1.5 times greater in area than the upfield band.[3] The refractive index of the oxathiolane (determined at 23 °C) had changed from 1.5571 to 1.5634; however, no changes were observed in the mass spectrum or elemental analysis. Similar results were noted with the oximino methyl ether (**3**, X = O; Y = S; R = CH_3) where the refractive index measured at 23 °C changed from 1.5587 to 1.5631. Heating the samples at reflux in nonpolar solvents (benzene, carbon tetrachloride, or carbon disulfide) for 30 min, however, produced no change in the NMR spectrum or refractive index. Apparently, in polar solvents, the product that forms initially undergoes thermal isomerization of the oxime (with or without the concomitant inversion at the asymmetric carbon atom). Isomerization was not observed in nonpolar solvents.

The possibility of simple acid-catalyzed isomerization of the imine was excluded by azeotropic distillation of a chloroform solution of **1** with *p*-toluenesulfonic acid or boron trifluoride. No changes were observed. Variation in ring conformation was ruled out as a possible explanation for the apparent anomalies in the spectra because it was not possible to cause coalescence of the methine peaks on heating. Attempts to resolve the geometric isomers by thin layer or gas–liquid chromatography, however, were unsuccessful.

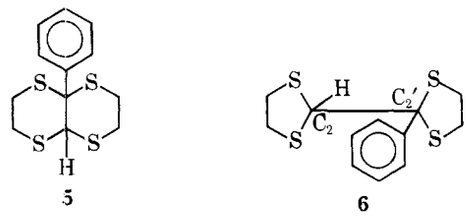
Assignment of structure of the isomers was tentatively made from chemical shifts, in a manner analogous to that in which configurational identification of isomeric benzaldoximes[4] was made; i.e., from the relative positions of the aldehydic proton absorption bands. The aldehydic proton is always deshielded in the syn form, and therefore appears at a lower field intensity than does the anti isomer. Similar shielding effects can be anticipated with 2-benzoyl-1,3-oxathiolane oxime *O*-alkyl ethers, resulting in the methine proton of the syn isomer (**4a**) absorbing downfield of the corresponding proton of the anti (**4b**) isomer. Accordingly, the major product of the condensation reaction is **4b**, in which the alkoxy group is trans to the



4a 4b

oxathiolane ring. Heating in polar solvents results in predomination of the cis (**4a**) isomer.

Reaction of **1** with ethanedithiol (**2**, X = Y = S) produced a yellow, crystalline product in which the alkoxyimino moiety was no longer present, as determined from an examination of the infrared spectrum. However, characteristic bands for C–S vibration (ν 655 cm^{-1}) were apparent. Low-resolution mass spectral data (obtained at 10 eV) indicated that the compound had a molecular weight of 286, which, with the elemental analysis, was shown to correspond to the molecular formula $C_{12}H_{14}S_4$. It was concluded that 2 mol of 1,2-ethanedithiol had combined with 2-alkoxyiminophenylacetaldehyde, forming either of two structural isomers: a *cis*-naphthodithiane, **5**, or 2-phenyl-2-[2-(1,3-dithiolano)]-1,3-dithiolane (**6**).



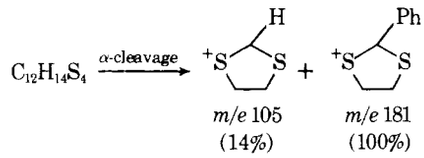
5 6

Elucidation of the structure of the $C_{12}H_{14}S_4$ compound was made by a mass spectrometric technique capable of distinguishing the pendant from the alternative fused ring system in the determination of the structure of glyoxal bisthioacetals.[5,6,7]

The major fragmentation pathway of the 2,2′-bis(1,3-dithiolanyl) derivative, **6**, involves α-cleavage of the molecular ion resulting in the loss of a 1,3-dithiolane ring fragment by homolysis of the C_2–$C_{2'}$ bond.

$C_{12}H_{14}S_4$ undergoes fission under electron impact at 10 eV[3] to generate the fragments shown in Scheme II. This mode of

Scheme II



fragmentation, giving rise to α-cleavage products (*m/e* 181, 105), clearly excludes the fused bicyclic structure, **5**. It must be concluded, then, that the reaction of 2-alkoxyiminophenylacetaldehydes, **1**, with 1,2-ethanedithiol yields 2-phenyl-2-[2-(1,3-dithiolano)]-1,3-dithiolane (**6**).

In conclusion, whereas both sulfur and oxygen nucleophiles react at the carbonyl carbon, only the thiol reacts at the imino carbon. The high nucleophilicity of the soft mercaptan base permits reaction at both the harder Lewis acid (i.e., carbonyl carbon) and softer acid (i.e., imino carbon). Hydroxyl groups are less nucleophilic, harder bases and tend to react at the harder electrophilic (carbonyl) center, rather than the imino carbon, a less reactive, softer acid.[8] Reaction at the imino carbon occurs exclusively with the more nucleophilic, softer sulfur-containing bases. The isomerization of the oxime observed during reaction of **1** with 2-mercaptoethanol may reflect reaction of the thiol moiety at the imino carbon to yield a transient thiocarbinolamine. The free hydroxyl group in this intermediate lacks the reactivity to cause cyclization (with loss of alkoxyamine) but rather eliminates the reactant to re-form the oxime with concomitant loss of stereochemical purity. These results are consistent with the fact that the aldehydic carbonyl group is more polar and generally more reactive toward nucleophilic attack than the corresponding imino function.

The dioxolane and oxathiolane derivatives were submitted for pharmacological testing, and all showed moderate antibacterial activity toward *S. aureus* (Smith strain) and *K. pneumoniae* (AD strain) in an in vivo test.

Experimental Section

Preparation of 2-alkoxyiminophenylacetaldehydes was carried out as previously described and products had physical properties identical with reported values.[1]

General Procedure for Preparation of Heterocyclic Derivatives. The optimum conditions varied from compound to compound, but a general procedure involved heating a benzene solution containing the aldehyde and a 10% molar excess of ethylene glycol, 2-mercaptoethanol, or ethanedithiol in a round-bottom flask equipped with a Dean-Stark trap and a condenser fitted with a calcium chloride for 20 min. Five milligrams of *p*-toluenesulfonic acid or 1 ml of boron trifluoride etherate was added and heating at reflux continued for 24–48 h. The cooled benzene solution was washed with ice-cold saturated $NaHCO_3$ solution, then water and dried over anhydrous magnesium sulfate. The dried solution was decanted and the benzene removed by distillation to yield either a solid which could be recrystallized or an oil which was then purified by distillation.

Registry No.—**1** (R = CH_3), 32349-36-3; **1** (R = C_2H_5), 32349-37-4; **2** (X = Y = O), 107-21-1; **2** (X = O; Y = S), 60-24-2; **2** (X = Y = S), 540-63-6.

Supplementary Material Available. Full NMR data for oxime isomerization studies (3 pages). Ordering information is given on any current masthead page.

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Thermodynamic pK_a's for the Second Ionization of Some Alkylphosphonic Acids[1]

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There is considerable current interest in determining the curvature of Brønsted plots.[2] A structurally homogeneous set of acid–base catalysts covering a wide pK_a range is required for this purpose, and it is useful also if these catalysts are reasonably transparent to ultraviolet and visible light, for then rate measurements may be made by the very convenient spectroscopic method now in widespread use. Unfortunately, many of the acids and bases commonly employed as catalysts fail to meet these requirements, and it is of interest therefore to develop new catalyst sets.

Simple aliphatic phosphonic acids show considerable promise in this respect. They are readily available, highly stable substances with no strongly chromophoric groups, and in their second dissociation