Anal. Calcd for $C_{21}H_{24}NO_2Cl$: C, 70.48; H, 6.76; N, 3.91. Found: C, 70.62; H, 6.84; N, 3.71.

Acknowledgment. The authors are grateful to the National Science Foundation (GP22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corporation of America are also gratefully acknowledged.

Registry No.—**2**, 50259-03-5; **11**, 50259-04-6; **15**, 5728-52-9; **16**, 50259-06-8; **18**, 50259-07-9; **19**, 50259-08-0; **20**, 50259-09-1; **21**, 19261-37-1; **22**, 50259-11-5; **23**, 50546-23-1; **24**, 20334-70-7; **30**, 50259-13-7; HMPA, 680-31-9.

References and Notes

(1) Part XXII of a study on the chemistry of 5,6-dihydro-1,3-oxazines. For previous papers in this series, see A. I. Meyers, A. C. Kovelesky, and A. J. Jurjevich, *J. Org. Chem.*, **38**, 2136 (1973).
(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.
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The Chemistry of 2-Chloromethyloxazines. Formation of Phosphoranes and Phosphonates. The Use of α,β-Unsaturated Oxazines as a Common Intermediate for the Synthesis of Aldehydes, Ketones, and Acids[1]

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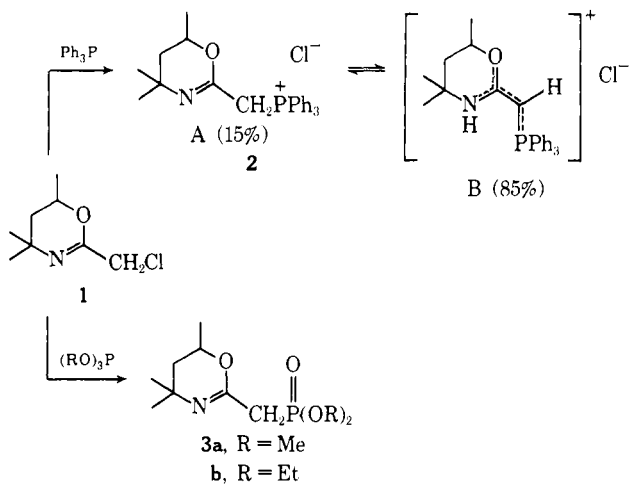
Received August 31, 1973

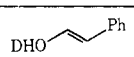
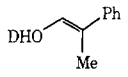
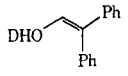
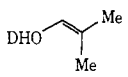
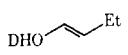
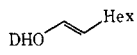
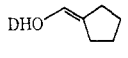
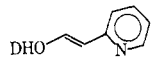
The 2-chloromethyloxazine **1** has been found to yield phosphonium salts **2** and phosphonates **3** which serve as "Wittig-type" reagents upon reaction with carbonyl compounds. The resulting α,β-unsaturated oxazines **5**, in turn, have been shown to serve as a common precursor to unsaturated aldehydes, ketones, and acids by (a) sodium borohydride reduction of **5** or their *N*-methyl quaternary salts **24**, (b) addition of organolithium reagents to the *N*-methyl quaternary salts **24**, and (c) hydrolysis of **24** in aqueous medium.

The availability of the 2-chloromethyloxazine **1** and its successful use of an electrophile[1] has prompted an investigation into its potential role as a precursor to oxazine "Wittig-type" reagents. Reaction of **1** with triphenylphosphine provided a 75% yield of the phosphonium salt **2** as a 1:5.7 mixture of tautomers A and B. The infrared spectrum of **2** (chloroform) showed only weak absorption at 1660–1670 cm^{-1} for the C=N link in A and strong absorption at 1603 cm^{-1}, whereas the ultraviolet spectrum (ethanol) exhibited bands at 273, 267, and 263 nm resulting from extended delocalization in B. The nmr spectrum of **2** showed a doublet at δ 4.22 (J = 15 Hz, 0.85 H) and a broad signal at δ 10.2 (0.85 H) attributable to the vinyl and NH protons, respectively, in the B tautomer. A small, broad signal at δ 2.48 was present due to the α-methylene protons in tautomer A. The highly delocalized structure in B was further confirmed by a single-crystal X-ray analysis.[3] The chloromethyloxazine also underwent a smooth Michaelis–Arbuzov reaction with trialkyl phosphites, furnishing the oxazine phosphonates **3a** (40%) and **3b** (80%). Both **2** and **3b** were allowed to react with a variety of carbonyl compounds in order to assess their ability to form olefinic derivatives.



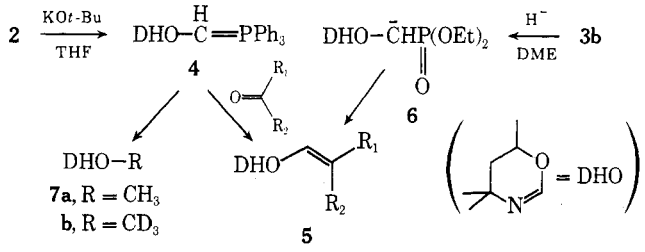
When a suspension of **2** in THF was treated with potassium *tert*-butoxide, a yellow solution of the phosphorane **4** formed immediately. The phosphorane reacted rapidly and exothermally with aldehydes, giving good yields of the *trans*-vinyl oxazines **5** (R_2 = H). Reactions with ketones were more sluggish, requiring overnight heating and resulting, where possible, in mixtures of geometric isomers

Table I
Coupling of Oxazines 2 and 3b with Carbonyl Compounds

R_1	R_2	Vinyl oxazine 5	Yield, % From 2	Yield, % From 3b	Bp, °C (mm)	λ (EtOH), nm (ε)	ν, cm⁻¹ (film)
Ph	H		94	80	110 (0.4)	274 (27,000)	1613 (s) 1644 (s)
Ph	Me		70[a]	57[b]	122 (1.5)	275 (22,000)	1611 (m) 1645 (s)
Ph	Ph		52	77	80[c]	275 (20,000)	1603 (s) 1636 (s)
Me	Me		50	73	55 (1.5)	222 (14,000)	1612 (s) 1645 (s) 1655 (s)
Et	H		80	75	56 (1.0)	212 (19,600)	1626 (s) 1653 (m) 1663 (s)
n-Hex	H		82	72	110 (1.3)	213 (16,000)	1620 (s) 1647 (m) 1664 (s)
$-(CH_2)_4-$			48	77	80 (0.5)		1608 (s) 1634 (s) 1658 (s)
2-C_5H_4N	H		72	65	128 (0.5)		1599 (m) 1613 (s) 1653 (s)

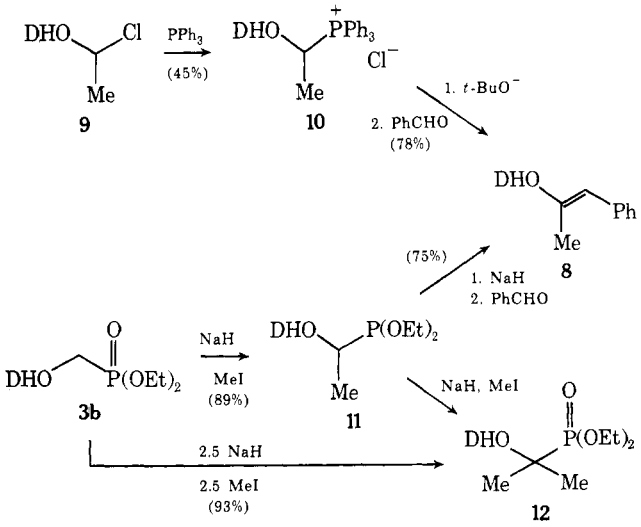
[a] 50:50 cis–trans mixture. [b] 24:76 cis–trans mixture. [c] Melting point.

(Table I). Furthermore, simple alkaline hydrolysis of the phosphorane 4 readily gave the 2-methyldihydroxazine **7a**.[4] When the hydrolysis was performed in D_2O–NaOD, a 70% yield of the 2-trideuteriomethyloxazine **7b** was isolated. This method, in which the deuterated oxazine can be obtained in quantity, should provide a route to tetradeuterioacetaldehyde[4] and other α-deuterioacetaldehyde derivatives. Treatment of the oxazine phosphonate **3b** with sodium hydride in dimethoxyethane cleanly produced the anion **6**. Its reaction with carbonyl compounds was found to be more efficient and occurred smoothly at room temperature, (Table I). The reaction of **6** with acetophenone gave a 24:76 mixture of **5**. The isomer containing the phe-

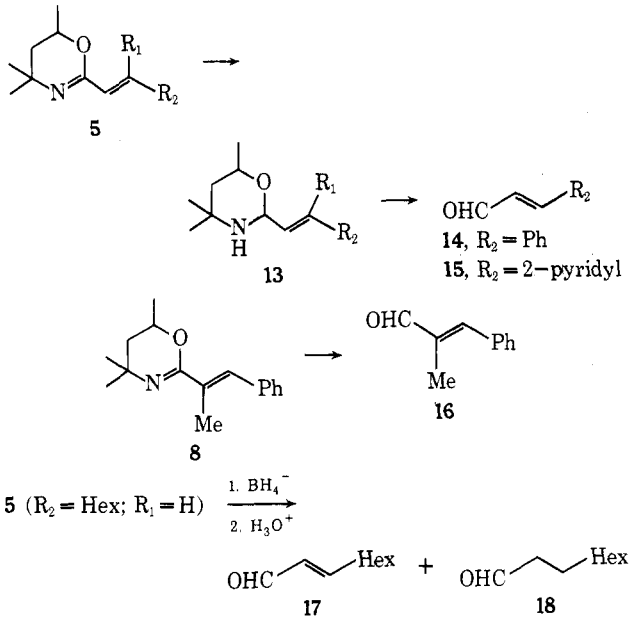


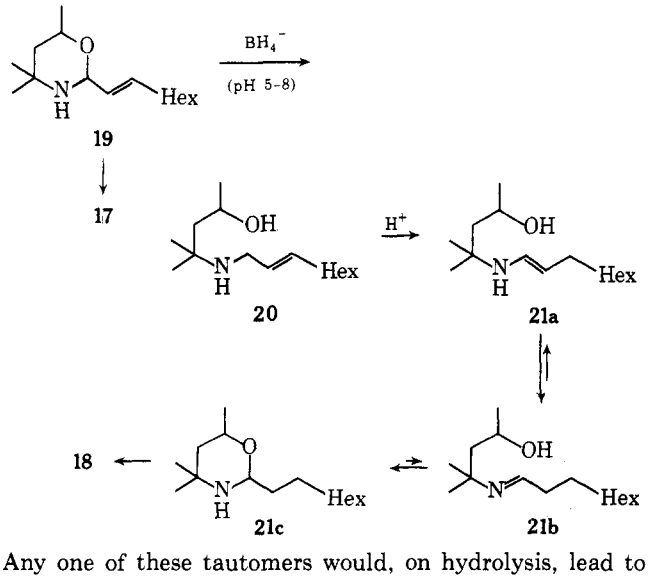
nyl group trans to the oxazine ring was the predominant product. The isomer ratio from acetophenone and **4** was approximately 50:50. On heating to 180° for 45 min, the mixture was brought to thermal equilibrium, furnishing a 15:85 cis-trans mixture. Thus, the oxazine phosphonate anion **6**, at room temperature, couples with ketones to give nearly thermodynamic products.

It was desired to extend the preparation of vinyl oxazines to the α-methyl derivative **8**. As stated previously,[1] the value of the oxazines in synthesis depends greatly on the degree to which the 2 substituent can be varied. Introduction of the α-methyl group (*i.e.*, **8**) would lead to α-methyl aldehydes, ketones, or acids. The preparation of **8**, as a suitable example to accomplish these goals, was successfully achieved *via* two routes. Conversion of the 2-(α-chloroethyl)oxazine **9**[1] to its phosphonium salt **10** took place upon heating with triphenylphosphine in xylene. The yield of **10** was 45% and examination of its spectral properties revealed that it represented a highly delocalized ion similar to the phosphonium salt **2**. Addition of potassium *tert*-butoxide followed by addition of benzaldehyde provided the trisubstituted olefin **8** in 78% yield. Attempts to increase the efficiency of this sequence by starting with the phosphonium salt **2** and generating **10** *in situ* led to mixtures containing **2** (35%) and **10** (65%) and ultimately to di- and trisubstituted oxazine olefins **5** (R_2 = H; R_1 = Ph) and **8**, respectively. Employing the oxazine phosphonate **3b**, the α-methyl derivative **11** was obtained by treating the anion of **3b** with 1 equiv of methyl iodide. Distillation gave the monomethyloxazine phosphonate in 89% yield and 5–8% of the dimethyloxazine phosphonate **12**. Alternatively, **12** could be prepared in 93% yield by treating **3b** with excess sodium hydride and methyl iodide. It may be concluded that the oxazine phosphonium salts **2** and **10** and phosphonates **3** and **11** are indeed useful precursors to di- and trisubstituted olefins containing the oxazine moiety.

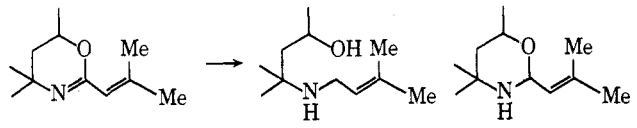


It now remained for the vinyl oxazines to demonstrate their prowess toward the preparation of carbonyl compounds. When the vinyl oxazines **5** (R = Ph, 2-pyridyl, R_1 = H) were subjected to the standard borohydride reduction,[4] the tetrahydro-1,3-oxazine **13** was produced and, without purification, hydrolyzed with aqueous oxalic acid to the α,β-unsaturated aldehydes **14** and **15.** This approach to 2-pyridylacrolein overcomes the previously reported difficulty[4] which failed to produce this compound. In a similar fashion, the oxazine **8** led to α-methylcinnamaldehyde **16** in 65% yield. On the other hand, the oxazine **5** (R = Hex), after reduction and hydrolysis, led to a 1:1 mixture of 2-nonenal (**17**) and nonanal (**18**). Examination of the nmr spectrum of the reduction product prior to hydrolysis revealed that a mixture of the expected product **19** and the overreduced product **21** was present. The latter is presumably formed by hydride attack on **19** (or the open-chain conjugated imine) in the weakly acidic medium (pH 5–8, −45°) affording the unsaturated amino alcohol **20** which rearranges to the enamine **21a,** capable of existing in tautomeric equilibrium with **21b** and **21c.**





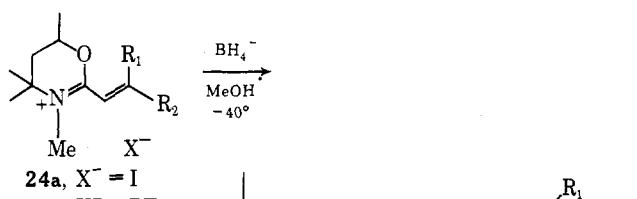
Any one of these tautomers would, on hydrolysis, lead to nonanal **18.** The possibility of sequential 1,4- and 1,2-hydride addition to **5** is also likely. However, the oxazine **5** (R_1 = R_2 = Me), when treated with sodium borohydride in weakly acidic medium (pH 5–7), gave **22** in 94% yield. This result would tend to substantiate the postulated route to nonanal (**19** → **18**) described above. The unsaturated amino alcohol **22** was found to be stable to acid solution even when heated in 3 *N* oxalic acid. Only a trace (~5%) of the desired aldehyde precursor **23** was detected

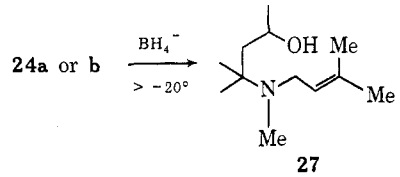


(nmr). It should also be noted that **5** (R = Hex) could be quantitatively transformed into **21** and ultimately to nonanal by performing the borohydride reduction at pH 3–5. The increased acidity in this experiment results in an enhancement of the reduction of **19** to **20.** It appears, therefore, that the conversion of vinyl oxazines **5** to α,β-unsaturated aldehydes by the standard reduction-hydrolysis technique is limited to aryl substituents on the olefin **5** (R = Ph, pyridyl, etc.). It was subsequently found that overreduction of aryl-substituted tetrahydro-1,3-oxazines **13** also occurred, albeit to a small degree (1–5%). Fortunately, rearrangement of these side products (*i.e.*, **20,** Hex = aryl) to the enamine (**21,** Hex = aryl) does not take place, as also noted for **22,** and saturated aldehydes do not contaminate the unsaturated derivatives.

In order to circumvent these undesirable side reactions, it would be necessary to by-pass both the labile tetrahydro-1,3-oxazine intermediates, **19** and **21,** and the acidic medium necessary for borohydride reduction. It is of interest to note again that the dihydrooxazines **5** and **8,** and the 2-alkyl derivatives reported earlier,[4] are virtually inert to sodium borohydride in neutral or strongly alkaline (pH >10) media.

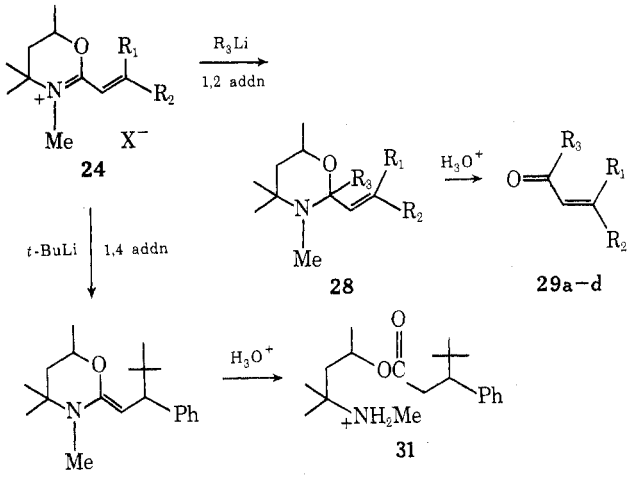
It was found that the *N*-methyl quaternary salts of the vinyl oxazines **24,** readily formed in high yield using either methyl iodide or trimethyloxonium fluoroborate, not only provided the solution to the above problem, but also served as a source of α,β-unsatrated ketones and acids. Both the iodide **24a** and the fluoroborate **24b** salts were reduced with sodium borohydride in methanol at −35 to −40° to the corresponding tetrahydro-1,3-oxazines in good yield. Acidic cleavage (oxalic acid) produced the α,β-unsaturated aldehydes **14** and **26** in 78 and 65% yields, respectively. Thus, **26,** which could not be prepared by reduction of the oxazine **5,** was readily formed *via* its *N*-methyl quaternary salt. That the reduction temperature (below −35°) was indeed critical was shown by the fact that the amino alcohol **27** was formed (~40%) when re-





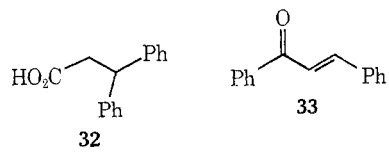
duction was performed at −20°. At 0°, the reduction of **24** gave **27** in 90% yield. Since reduction of the *N*-methyl salts gave **25** at low temperature and **25** cannot engage in ring–chain tautomerism as in the case of **21**, the route by which **27** is formed must involve direct hydride attack on the 2 position of the tetrahydro-1,3-oxazine.

As already stated, the synthetic utility of the *N*-methyl quaternary salts **24** was not limited to α,β-unsaturated aldehydes. Reaction of **24** with various organolithium reagents led to the adducts **28** which generated the α,β-unsaturated ketones **29** after hydrolysis in oxalic acid. The

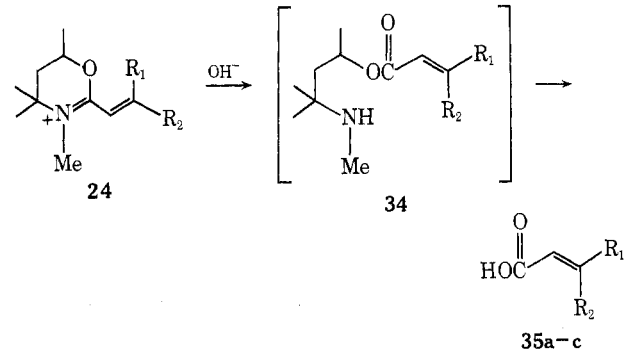


	R_3	R_1	R_2
a	Me	H	Ph
b	Et	Me	Me
c	*t*-Bu	H	Ph
d	Et	$-(CH_2)_4-$	

overall conversion, based upon the vinyl oxazines **5**, was in the range of 50–80% except for the ketone **29c** derived from *tert*-butyllithium addition. The bulky nature of this reagent resulted in addition to **24** in both a 1,2 and 1,4 fashion (**28** and **30**, respectively). The *tert*-butyl ketone was isolated after hydrolysis of **28** in 20% yield. The 1,4-addition product **30**, also present during the acidic hydrolysis, led only to the amino ester **31** and did not interfere with the isolation of the *tert*-butyl ketone. Similar behavior of ketene *N,O*-acetals related to **30** has been previously observed[5] and their ester derivatives (**31**) serve as precursors to carboxylic acids and esters by hydrolysis or transesterification. Phenylmagnesium bromide gave almost exclusive 1,4 addition to **24** (R_1 = H; R_2 = Ph), providing, after hydrolysis, an 80% yield of β,β-diphenylpropionic acid (**32**) and only a trace of chalcone **33**. It then became

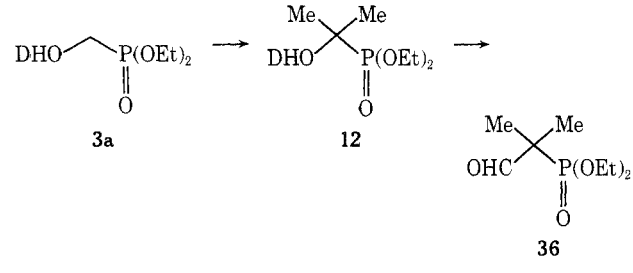


quite evident that the *N*-methyl quaternary salts also provide viable routes to carboxylic acids, simply by treatment with aqueous sodium hydroxide. Thus, **24**, on addition to dilute alkali, was found to immediately and quantitatively open to the amino ester **34**. These intermediates could be isolated and characterized and subsequently cleaved to the α,β-unsaturated acid, usually in alcoholic aqueous base. In a related study,[6] amino esters of the type **34** were shown to be readily transformed into their methyl esters by heating in methanol containing a catalytic amount of *p*-toluenesulfonic acid.



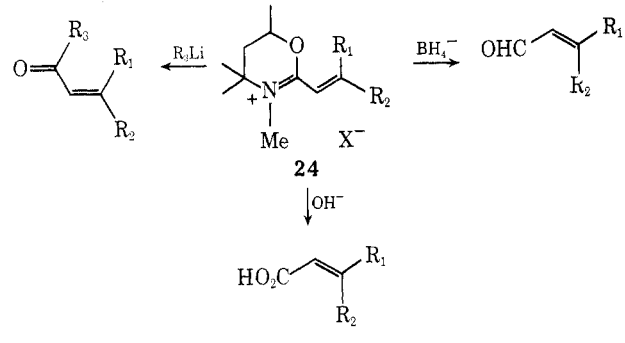
	R_1	R_2
a	Me	Me
b	Ph	H
c	$-(CH_2)_4-$	

As previously mentioned, the alkylation of **3b** with excess methyl iodide gave a high yield of the dimethyloxazine phosphonate **12**. Reduction with sodium borohydride (−40°, pH 5), after oxalic acid hydrolysis, produced the phosphonate aldehyde **36** in 62% overall yield. Thus, an entry into phosphorous-substituted aldehydes should also be feasible.



In summary, the oxazine phosphoranes and phosphonates serve as ready precursors to a variety of 2-vinyl oxazines and the latter, *via* their *N*-methyl quaternary salts (**24**), provide a common intermediate for preparing α,β-unsaturated aldehydes, ketones, and carboxylic acids (Scheme I).

Scheme I



Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.; Midwest Microlabs, Inc., Indianapolis, Ind.; and Atlantic Microlabs, Inc., Atlanta, Ga. Infrared spectra were determined on a Perkin-Elmer 257 grating spectrophotometer. The nmr spectra were measured with Varian A-60A and T-60 instruments using carbon tetrachloride or deuteriochloroform as solvent containing tetramethysilane (~1%) as the internal standard. Mass spectra were obtained on an Atlas CH-4 spectrometer at 70 eV.

Oxazine Phosphonium Chloride 2. A solution of 2-chloromethyloxazine[1] **1** (44.1 g, 0.25 mol) and triphenylphosphine (91 g, 0.35 mol) in benzene (500 ml) was heated with stirring at reflux for 32 hr. The mixture was cooled, and the salt was filtered, washed

Table II
Elemental Analysis for Vinyl Oxazines 5

R_1	R_2	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Ph	H	78.56	8.35	6.11	78.46	8.62	6.03
Ph	Me	78.97	8.70	5.76	78.68	8.65	5.86
Ph	Ph	82.59	7.59	4.59	82.54	7.62	4.71
Me	Me	72.88	10.56	7.73	72.99	10.76	7.65
Et	H	72.88	10.56	7.73	72.74	10.54	7.83
n-Hex	H	75.90	11.46	5.90	75.63	11.50	5.86
$-(CH_2)_4-$		75.32	10.21	6.76	75.48	10.06	6.80
2-C_5H_4N	H	73.01	7.88	12.16	72.85	7.61	11.92

three times with dry ether, and dried under vacuum. The reaction gave 77 g (70%) of **2**. The product could be recrystallized from acetonitrile–ether: mp 224°; uv (EtOH) 273, 267, 263 nm; ir (KBr) 1603 cm^{-1}; nmr ($CDCl_3$) δ 7.45 (m, 15), 4.22 (d, 0.85, J = 15 Hz, exchanges with D_2O), 10.2 (b, 0.85, exchanges with D_2O), 1.42 (d, 6), 0.81 (d, 3).

Anal. Calcd for $C_{25}H_{29}NPCl$: C, 70.50; H, 6.86; N, 3.29. Found: C, 70.63; H, 6.76; N, 3.24.

Vinyl Oxazines 5 from Oxazine Phosphonium Salt 2. The phosphonium chloride **2** (8.76 g, 0.02 mol) was suspended in THF (35 ml) and to this suspension was added freshly sublimed potassium *tert*-butoxide (2.24 g, 0.02 mol). A yellow solution of the phosphorane **4** formed immediately. The solution showed uv absorption at 342 nm and was used in the subsequent reactions.

Aldehydes were added dropwise to the solutions prepared above and the mixture was allowed to stir for 4 hr (ketones were refluxed for 18 hr). The mixture was poured into water, made acidic (pH ~3), and extracted with benzene and the benzene extracts were discarded. The aqueous acid solution was neutralized with sodium bicarbonate and extracted with ether. The ether solution was concentrated and the residue was applied to a neutral alumina column (Woelm, activity I) and eluted with ether–pentane (1:1). Yields and pertinent data are listed in Table I. Elemental analyses are given in Table II.

2-Trideuteriomethyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (7b). Phosphonium salt **2** (8.75 g, 0.02 mol) was added to D_2O (20 ml) and the suspension was allowed to stir for 30 min. Ten milliliters of 20% NaOD in D_2O was added and the mixture was allowed to stir for 15 min. The product was extracted with ether–pentane (1:3) and dried over potassium carbonate. The extracts were evaporated and the residue was distilled to give 2.2 g (70%) of **7b**: bp 47° (17 mm); ir 2220, 1660 cm^{-1}; m/e 144. The methyl singlet at δ 1.77 was barely visible.[4]

2-(Diethylphosphonomethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (3b). The chloromethyloxazine **1** (44.1 g, 0.25 mol) was added to triethyl phosphite (100 g) and the solution was refluxed vigorously for 24 hr. The solution was then distilled under vacuum (0.1 mm) and the oxazine phosphonate **3b**, bp 109° (0.075 mm), was collected. The reaction gave 55 g (80%) of a pale yellow liquid: ir 1660, 1260, 1050, 960 cm^{-1}; nmr (CCl_4) δ 3.8–4.4 (m, 5), 2.6 (d, 2, J = 21 Hz), 1.8 (d of t, 2), 1.3 (t, 6), 1.2 (d, 3), 1.1 (s, 6).

Anal. Calcd for $C_{12}H_{24}NO_4P$: C, 51.99; H, 8.73; N, 5.06. Found: C, 52.01; H, 8.70; N, 5.12.

2-(Dimethylphosphonomethyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (3a) was prepared as described above using trimethyl phosphite. The reaction gave **3a** in 45% yield: bp 102° (1 mm); mp 56–57° [petroleum ether (bp 30–60°)]; ir 1660, 1260 cm^{-1}; nmr (CCl_4) δ 4.2 (m, 1), 3.8 (d, 6, J = 12 Hz), 2.6 (d, 2, J = 22 Hz), 1.7 (d of t, 2), 1.4 (d, 3), 1.2 (s, 6).

Anal. Calcd for $C_{10}H_{20}NO_4P$: C, 48.20; H, 8.10; N, 5.62. Found: C, 47.98; H, 8.22; N, 5.48.

Vinyl Oxazines 5 from Oxazine Phosphonate 3b. Oxazine phosphonate **3b** (5.54 g, 0.02 mol) was added to a stirred suspension of sodium hydride (1.0 g of a 56% dispersion, 0.022 mol) in 30 ml of 1,2-dimethoxyethane (DME). The evolution of hydrogen at 25° was complete after 2.5 hr and the resulting yellow solution was treated with 0.22 mol of aldehyde or ketone. Stirring was continued for 4 hr at room temperature, the mixture was poured into ice–water, acidified (1 *N* HCl), and extracted with petroleum ether, and the extracts were discarded. The aqueous solution was made basic (pH ~9) and the vinyl oxazine **5** was recovered by ether extraction, concentration, and distillation (*cf.* Table I).

Phosphonium Salt 10. A solution of 19.0 g (0.1 mol) of **9**[1] and 35 g (0.13 mol) of triphenylphosphine in 150 ml of xylene was heated to reflux for 48 hr. Isolation of **10** was accomplished as previously described for **2**. The salt **10**, mp 241° (acetonitrile–ether), was formed in 45% yield (18.0 g): ir (KBr) 1600 cm^{-1}; nmr ($CDCl_3$) δ 9.0 (b, exchangeable with D_2O), 5.2 (b, exchangeable with D_2O), 7.4–8.2 (m, 15).

Anal. Calcd for $C_{27}H_{31}NOPCl$: C, 71.74; H, 6.91; N, 3.10. Found: C, 71.80; H, 6.99; N, 3.27.

Phosphonate 11. The sodium salt of **3b** prepared as above was treated with 1 equiv of methyl iodide and the mixture was stirred overnight. The mixture was poured into water and extracted with ether. Evaporation and distillation gave **11** (89%): bp 97° (0.1 mm); ir (film) 1660, 1260 cm^{-1}; nmr (CCl_4) δ 4.1 (m, 5), 2.5 (m, 1, J = 23 Hz), 1.1–1.8 (m, 20).

Anal. Calcd for $C_{13}H_{26}NO_4P$: C, 53.60; H, 9.00. Found: C, 53.92; H, 9.22.

2-(1-Phenylpropen-2-yl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (8) was prepared from phosphonium salt **2** in 78% yield and from phosphonate **3b** in 75% yield according to the procedures already outlined using these reagents: bp 80° (0.05 mm); uv (EtOH) 261 nm (ϵ 20,000); ir (film) 1620, 1635 cm^{-1}; nmr (CCl_4) δ 7.3 (s, 6), 4.1 (m, 1), 2.0 (d, 3, J = 1.5 Hz), 1.7 (d of t, 2), 1.4 (d, 3), 1.1 (s, 6).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.00; H, 8.55; N, 5.73.

Oxazine Phosphonate 12. The sodium salt of **3b** was prepared in the manner described for the preparation of **11** except that 2.5 equiv of sodium hydride was employed. Addition of 2.5 equiv of methyl iodide followed and the solution was stirred overnight. The reaction gave **12** in 93% yield: bp 110° (0.5 mm); ir (film) 1660, 1260 cm^{-1}; nmr (CCl_4) δ 4.05 (m, 1), 4.95 (pentet, 4), 1.6 (d of t, 2), 1.4 (d, 3), 1.3 (t, 6), 1.1 (s, 6), 1.15 (s, 6).

Anal. Calcd for $C_{14}H_{28}NO_4P$: C, 55.07; H, 9.25; N, 4.59. Found: C, 54.96; H, 9.33; N, 4.80.

Diethyl 1-Formyl-1-methylethylphosphonate (36). Reduction of the oxazine phosphonate **12** using sodium borohydride (−45°, pH 5–7) as previously described[4] followed by heating in oxalic acid (2 hr) gave an aqueous mixture which was extracted with ether. Distillation of the ether residue gave **36** in 65% yield: bp 62° (0.4 mm); ir (film) 2720, 1720, 1250 cm^{-1}; nmr (CCl_4) δ 9.6 (d, 1, J = 2 Hz), 4.1 (pentet, 4), 1.4–1.2 (d, t, 12).

Anal. Calcd for $C_8H_{17}PO_4$: C, 46.15; H, 8.24. Found: C, 46.20; H, 8.00.

Aldehydes from Vinyl Oxazines 5. The following aldehydes were prepared from the indicated vinyl oxazine **5** by the general borohydride reduction–oxalic acid hydrolysis procedures described previously[4] on a 40-mmol scale.

Cinnamaldehyde (14) was prepared in yields of 50–75% from **5** (R_1 = Ph; R_2 = H). Yields appeared to be dependent upon the pH of the borohydride reduction step. The pH was varied in several runs from 5 to 9. Best results were obtained with an apparent pH of 7. The product formed a semicarbazone, mp 206–207° (lit.[7] mp 208°).

3-(2-Pyridyl)acrolein (15) was prepared in 45% yield from **5** (R_1 = C_5H_5N; R_2 = H). The product was isolated by neutralization of the oxalic acid solution with sodium bicarbonate and extraction of the product with ether. The product **15** had mp 42° (hexane) (lit.[8] mp 43°); ir (film) 2760, 1670 cm^{-1}.

2-Methyl-3-phenylacrolein (16) was prepared from **8** in 65% yield. The product formed a semicarbazone, mp 207° (lit.[7] mp 207–208°).

A 50:50 Mixture of 2-Nonenal (17) and Nonanal (18) was prepared from **5** (R_1 = R_2 = H) in 61% yield. The products were collected from vpc using 10% SE-31 on Diatoport S at 100° and identified by the melting points of their respective 2,4-dinitrophenylhydrazones. 2-Nonenal[7] and nonanal[7] gave derivatives which melted at 126 and 106°, respectively.

Reduction of 5 (R_1 = R_2 = Me) to 22. Treatment of 3.62 g (0.02 mol) of **5** with aqueous sodium borohydride (−45°, pH 5–7) according to the standard procedure[4] gave, after extraction with ether, 3.43 g (94%) of **22**: bp 80° (0.3 mm); ir (film) 3260 cm^{-1}; nmr (CCl_4) δ 5.2 (t, 1), 3.9 (m, 1), 3.1 (d, 2), 1.6 (s, 3), 1.7 (s, 3), 0.9–1.5 (d, s, m, 13); NH, OH protons exchangeable with D_2O were masked in the latter region of the spectrum.

Anal. Calcd for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.01; H, 12.49; N, 7.80.

***N*-Methyl Salts 24a and 24b (R_1 = H; R_2 = Ph). A. Methiodide 24a.** Treatment of **5** (R_1 = H; R_2 = Ph) with excess methyl iodide in a small amount of ether with gentle warming for 18 hr in the dark resulted in a 96% yield of **24a**. The product was washed with ether for use in subsequent reactions. Recrystallization from acetonitrile–ether resulted in yellow needles, mp 223–224°, ir 1590, 1635 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}NOI$: C, 51.76; H, 5.97; N, 3.77. Found: C, 52.06; H, 6.12; N, 3.85.

B. Methyl Fluoroborate 24b. Treatment of **5** (R_1 = H; R_2 = Ph) with 1.5 equiv of trimethyloxonium fluoroborate in methylene chloride cooled to 0° for 30 min resulted in a 93% yield of the salt, which was isolated by filtering the methylene chloride solution, removal of the solvent, and recrystallizing from acetonitrile–ether to give colorless plates, mp 164°, ir 1590, 1634 cm^{-1}.

Anal. Calcd for $C_{16}H_{22}NOBF_4$: C, 58.03; H, 6.70; N, 4.23. Found: C, 57.99; H, 6.52; N, 4.53.

***N*-Methyl Salt 24a (R_1 = R_2 = Me).** The salt was prepared as above using excess methyl iodide and crystallized in quantitative yield. The salt was recrystallized from acetonitrile–ether to give colorless needles, mp 202°, ir 1574, 1625 cm^{-1}.

Anal. Calcd for $C_{12}H_{22}NOI$: C, 44.59; H, 6.87; N, 4.33. Found: C, 44.65; H, 6.90; N, 4.37.

Reduction of *N*-Methyl Salt 24a (R_1 = R_2 = Me) with Sodium Borohydride at 0°. The methiodide salt **24a** (6.46 g, 0.02 mol) was dissolved in absolute methanol (20 ml) and the solution was cooled to −30°, and to this solution was added, dropwise, sodium borohydride (0.02 mol) dissolved in a minimum amount of water. The solution was allowed to warm to 0° during a 1-hr period, 50 ml of cold water was added, the product was extracted with ether, and the ether extracts were washed with brine and dried (Na_2SO_4). Evaporation and distillation of the residue gave 5.41 g (90%) of **27**: bp 50° (0.05 mm); ir 3220 cm^{-1}; nmr (CCl_4) δ 5.9 (br s, 1, exchangeable with D_2O), 5.2 (t, 1), 4.0 (m, 1), 3.1 (m, 2), 2.2 (s, 3), 1.7 (s, 3), 1.8 (s, 3).

Anal. Calcd for $C_{12}H_{25}NO$: C, 72.31; H, 12.64; N, 7.03. Found: C, 72.28; H, 12.63; N, 6.79.

Reduction of *N*-Methyl Quaternary Salts 24a and 24b. Preparation of Aldehydes 14 and 26. The following *N*-methyl tetrahydrooxazines **25** were prepared by reduction of the corresponding *N*-methyl salts using sodium borohydride in methanol. The methanol solution was cooled (−45 to −35°) and this temperature was maintained throughout the reaction (30 min). Excess borohydride was destroyed at −45° by the addition of dilute hydrochloric acid. The solution was then made basic and the product was isolated by ether extraction. Drying and concentration of the extracts followed by distillation furnished the products.

The tetrahydrooxazine **25** (R_1 = H; R_2 = Ph) was prepared from **24a** (98%, 85% distilled) and from **24b** (93%): bp 95° (0.05 mm); ir 3100–3480, 1628, 1600 cm^{-1}; nmr (CCl_4) δ 7.0–7.6 (m, 5), 5.8 (d of d, 1), 6.7 (d, 1), 4.8 (d, 1), 3.8 (m, 1), 2.2 (s, 3), 0.8–1.8 (m, 11).

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.26; H, 9.33; N, 5.46.

The product was hydrolyzed to cinnamaldehyde using aqueous oxalic acid (reflux 2 hr) in 78% yield.

The tetrahydrooxazine **25** (R_1 = R_2 = Me) was prepared from **24a** (95%). The crude product **25** was hydrolyzed to 3-methyl-2-butenal (**26**) by oxalic acid in 65% yield. The aldehyde **26** formed a semicarbazone, mp 222° (methanol) (lit.[7] mp 221–222°).

Preparation of Ketones 29 from *N*-Methyl Salts of Vinyl Oxazines 24. To a suspension of the *N*-methyl iodide or fluoroborate (0.02 mol) in 20 mol of THF cooled to 0° was added a solution of the organometallic reagent (Grignard reagent or organolithium reagent, 0.022 mol) by drops; 2 hr was allowed for complete reaction. The solution was poured onto ice and then extracted with ether. The ether extracts were dried (K_2CO_3) and evaporated to give the intermediate **28** which was directly subjected to oxalic acid cleavage as described previously.

The following ketones were prepared by this general procedure from the indicated starting materials.

4-Phenyl-2-buten-2-one (29a) was prepared from methyllithium and **24a** (R_1 = H; R_2 = Ph) as described above in 82% yield. The product formed a semicarbazone, mp 176° (lit.[7] mp 177.5°).

4,4-Dimethyl-1-phenyl-1-penten-3-one (29c) was prepared from *tert*-butyllithium (solution in pentane) and **24a** (R_1 = H; R_2 = Ph) in 20% yield. The product had mp 43° (lit.[7] mp 43°).

5-Methyl-4-hexen-3-one (29b) was prepared from ethyllithium and **24a** (R_1 = R_2 = Me) in 55% yield. The product formed a semicarbazone, mp 160° (ethanol–water) (lit.[7] mp 162°).

4-Cyclopentylidine-3-butanone (29d) was prepared from **5** [R_1 = R_2 = $-(CH_2)_4-$] by preparing, *in situ*, the *N*-methiodide salt **24a**, removing the excess methyl iodide *in vacuo*, and addition of a solution of ethyllithium in THF. The crude adduct **25** was hydrolyzed without further purification to the ketone **29d** (55%), bp 96° (20 mm), semicarbazone mp 171° (lit.[9] mp 170–171°).

Preparation of Carboxylic Acids 35 from *N*-Methyl Salts of Vinyl Oxazines 24a. The methiodide salts **24a** were dissolved in cold water and the solution was rendered alkaline (pH ~10). After stirring for 10 min, the solutions were heated to reflux (3–4 hr) and reacidified. Extraction of the aqueous solution with ether afforded the carboxylic acids **35**. In this fashion β,β-dimethylacrylic acid (**35a**, 68%, mp 70°), cinnamic acid (**35b**, 92%, mp 131°), and cyclopentylideneacetic acid (**35c**, 87%, mp 64°) were obtained.

Amino Ester 34 (R_1 = R_2 = Me). The methiodide salt **24a** (6.46 g, 0.02 mol) was dissolved in cold water (25 ml) and the solution was made basic (pH ~10) for 10 min. The product was extracted with ether, and the ether extracts were dried (K_2CO_3) and evaporated to give on distillation 3.93 g (92%) of **34**, bp 75° (0.1 mm), ir 1710, 1650 cm^{-1}.

Anal. Calcd for $C_{12}H_{23}NO_2$: C, 67.57; H, 10.87; N, 6.57. Found: C, 67.54; H, 11.03; N, 6.77.

On heating in aqueous dilute sodium hydroxide (1.5 *N*) for 4 hr, the amino ester produced β,β-dimethylacrylic acid (**35a**) in 80% yield.

Acknowledgment. The authors are grateful to the National Science Foundation (GP 22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corp. of America are also gratefully acknowledged.

Registry No.—**1**, 50259-03-5; **2**, 50259-42-2; **3a**, 50259-43-3; **3b**, 50431-01-1; **5** (R_1 = Ph; R_2 = H), 50259-44-4; *cis*-**5** (R_1 = Ph; R_2 = Me), 50259-45-5; *trans*-**5** (R_1 = Ph; R_2 = Me), 50259-46-6; **5** (R_1 = R_2 = Ph), 50259-47-7; **5** (R_1 = R_2 = Me), 50259-48-8; **5** (R_1 = Et; R_2 = H), 50259-49-9; **5** (R_1 = *n*-Hex; R_2 = H), 50259-50-2; **5** [R_1, R_2 = $-(CH_2)_4-$], 50259-51-3; **5** (R_1 = 2-C_5H_4N; R_2 = H), 50259-52-4; **7b**, 50259-53-5; **8**, 50259-54-6; **9**, 50259-07-9; **10**, 50259-56-8; **11**, 50259-57-9; **12**, 50259-58-0; **17** 2,4-DNPH, 18287-00-8; **18** 2,4-DNPH, 2348-19-8; **22**, 43152-87-0; **24a** (R_1 = H; R_2 = Ph), 50259-62-6; **24a** (R_1 = R_2 = Me), 50259-63-7; **24b** (R_1 = H; R_2 = Ph), 50262-97-0; **25** (R_1 = H; R_2 = Ph), 50546-26-4; **27**, 50259-64-8; **29d**, 50259-65-9; **34** (R_1 = R_2 = Me), 50259-66-0; **36**, 35078-65-0.

References and Notes

(1) Part XXIII of a study on 5,6-dihydro-1,3-oxazines. For previous papers in this series see G. R. Malone and A. I. Meyers, *J. Org. Chem.*, **39**, 618 (1974).
(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.
(3) We thank Professor L. M. Trefonas of Louisiana State University in New Orleans for this determination. The details of this work will be published elsewhere. The projection formula and data for bond lengths and angles may be found in the Ph.D. Thesis of G. R. Malone, Wayne State University, 1972.
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