stoppered bottle and maintained at the kinetic temperature until completion. After concentration of the benzenic solution to small volume, the corresponding 2-thiophenecarboxanilide precipitated was filtered, washed free from aniline hydrochloride with water, dried, and recrystallized from suitable solvent. In all cases the amount of 2-thiophenecarboxanilide was ≥95% of that expected from the formation of 1 mol of anilide per 1 mol of acid chloride consumed. The mixture melting points with authentic samples of 2-thiophenecarboxanilides revealed no depression. Physical constants of 2-thiophenecarboxanilides are listed in Table VIII.

Registry No.—2-Thenoyl chloride, 5271-67-0.

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The Synthesis of Aldehydes from Dihydro-1,3-oxazines

A. I. MEYERS,* A. NABEYA, H. W. ADICKES, I. R. POLITZER, G. R. MALONE, A. C. KOVELESKY, R. L. NOLEN, AND R. C. PORTNOY

Department of Chemistry, Louisiana State University in New Orleans, New Orleans, Louisiana 70122 and Wayne State University, Detroit, Michigan 48202

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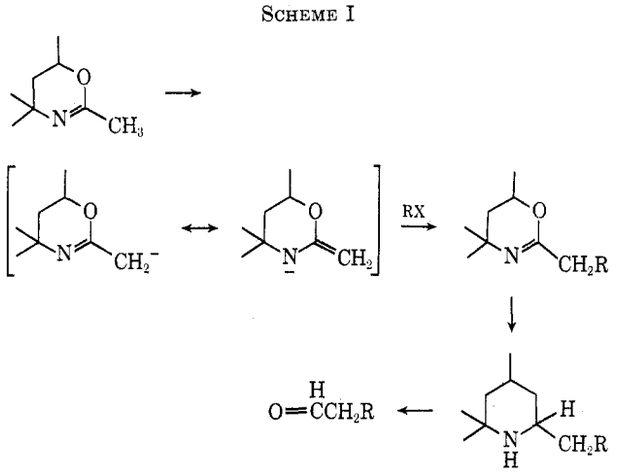
The use of readily available dihydro-1,3-oxazines (DHO) as precursors to substituted acetaldehydes, α,β-unsaturated aldehydes, cycloalkanecarboxaldehydes, and a variety of functionalized aldehydes is reported. The method is useful for both a two-carbon homologation of electrophiles to aldehydes as well as a three-carbon homologation of nucleophiles (RMgX, malonates, enamines). The scope and limitations of this synthesis are discussed.

In 1969, a series of brief reports[2-4] appeared which outlined a technique for the preparation of aldehydes based upon the dihydro-1,3-oxazine (DHO) ring system, and this is depicted in Scheme I. It is now

SCHEME I

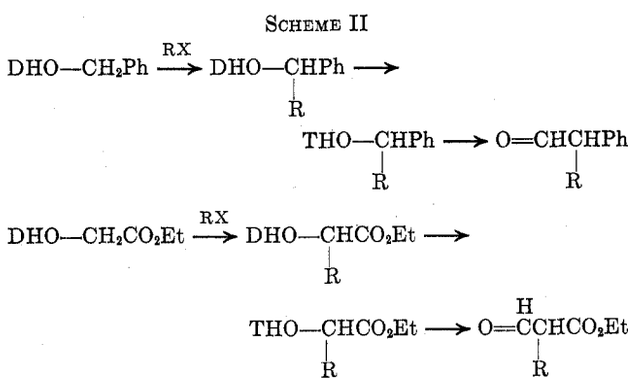


desirable to describe in detail the studies which led to the successful implementation of this process. The anticipated approach required that (a) a readily available dihydro-1,3-oxazine be utilized as starting material, (b) a stable carbanion be generated by the use of some suitable base, (c) reaction of the carbanion with carbon electrophiles lead only to C-alkylation, since N-alkylation would result in an undesirable side product, (d) a mild and efficient reduction be employed to reduce the C=N link in the sensitive oxazine ring, and (e) hydrolytic cleavage conditions be utilized to generate the aldehydic product from the tetrahydro-1,3-oxazine (THO).

The scheme would, in effect, be a two-carbon homologation of electrophiles to aldehydes and may be considered as the *aldehyde equivalent* to the malonic ester synthesis. A similar concept has been reported by Stork[5] utilizing metalated enamines which were alkylated by alkyl halides and hydrolyzed to produce the elaborated aldehyde, whereas a one-carbon homologation of electrophiles was described by Corey and Seebach[6] employing the versatile lithiodithiane system.

Oxazine systems which possessed 2 substituents other than methyl were also viewed as candidates for this sequence and are shown in Scheme II. Thus, the use of

SCHEME II



the 2-benzyl or the 2-carboethoxymethyl oxazines could serve as precursors to α-phenyl and α-carboethoxy aldehydes, respectively. Furthermore, the 2-vinyldihydro-1,3-oxazine was examined (Scheme III) to determine if it was suitable as a three-carbon homolog for organometallics. Recently, there have been reports from Walborsky[7] and this laboratory[8] which allow a

(1) Department of Chemistry, Colorado State University, Fort Collins, Colorado 80521.

(2) (a) A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969); (b) A. I. Meyers, H. W. Adickes, I. R. Politzer, and W. N. Beverung, *ibid.*, **91**, 765 (1969).

(3) A. I. Meyers, A. Nabeya, I. R. Politzer, H. W. Adickes, J. M. Fitzpatrick, and G. R. Malone, *ibid.*, **91**, 764 (1969).

(4) H. W. Adickes, I. R. Politzer, and A. I. Meyers, *ibid.*, **91**, 2155 (1969).

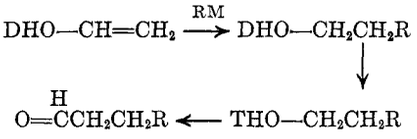
(5) G. Stork and S. R. Dowd, *ibid.*, **85**, 2178 (1963); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.*, 3976 (1970).

(6) E. J. Corey and D. Seebach, *Angew. Chem., Int. Ed. Engl.*, **4**, 1075 (1965); for a review of this subject, *cf.* D. Seebach, *Synthesis*, **1**, 17 (1969).

(7) H. M. Walborsky and G. E. Niznik, *J. Amer. Chem. Soc.*, **91**, 7778 (1969); **92**, 6675 (1970).

(8) A. I. Meyers and E. W. Collington, *ibid.*, **92**, 6676 (1970).

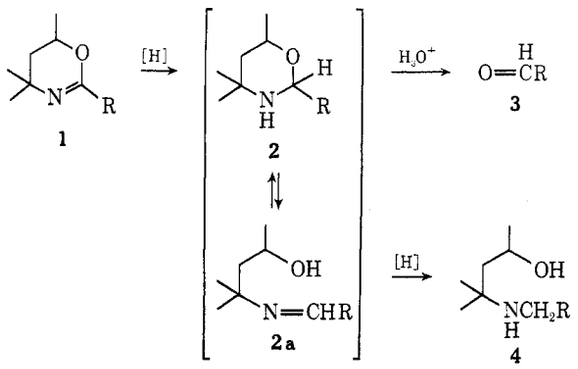
SCHEME III



one-carbon homologation of organometallics to aldehydes.

In the following discussion, the studies to achieve the goals set forth are presented along with examples of a variety of aldehydes which demonstrate the success of this effort.

Reduction of Dihydro-1,3-oxazines.—In a preliminary communication,[9] the ability of 5,6-dihydro-1,3-oxazines (**1**) to serve as precursors to aldehydes has been described. This was accomplished by pH-controlled reduction of the C=N link in **1**, affording the tetrahydro-1,3-oxazine **2** followed by hydrolysis to the aldehyde **3**. Owing to the well-known ring–chain tautomerism of tetrahydro-1,3-oxazines (**2**, **2a**) and related systems,[10] clean reduction of **1** could not be carried out by the usual means (catalytic or metal hydride[11]). The presence of the imine form **2a** and



the susceptibility of **2** to further reduction constantly led to a mixture containing considerable quantities of the amino alcohol **4**. A study was undertaken to determine if **1** could be reduced under conditions which would retard formation of the amino alcohol **4**, and thus introduce the dihydro-1,3-oxazine system as a valuable source of aldehydes. From previous efforts in these laboratories, the use of pH control during borohydride reductions was observed to be compatible with the formation of sensitive groups (**5** → **6**, **7** → **8**).[12–14] The 2-ethyldihydro-1,3-oxazine (**9**) was therefore chosen as the subject of a temperature and pH study in order to achieve the intended goal. At various temperatures and pH ranges (Table I) in ethanol–tetrahydrofuran containing aqueous acid or alkali, the borohydride reductions led to varying mixtures of tetrahydro-1,3-oxazines **10** and amino alcohols **11**. As can be seen from the results in Table I, only at −40° was

(9) A. I. Meyers and A. Nabeya, *Chem. Commun.*, 1163 (1967).

(10) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **64**, 1503 (1942); E. D. Bergman, E. Zinkin, and S. Pinchas, *Recl. Trav. Chim. Pays-Bas*, **71**, 168 (1952); A. F. McDonagh and H. E. Smith, *J. Org. Chem.*, **33**, 1 (1968); J. V. Paukstelis and R. M. Hammaker, *Tetrahedron Lett.*, **No. 32**, 3557 (1968); L. C. Dorman, *J. Org. Chem.*, **32**, 255 (1967); R. Kotani, T. Kuroda, T. Isozaki, and S. Sumoto, *Tetrahedron*, **25**, 4743 (1969).

(11) E. Schenker, *Angew. Chem.*, **73**, 81 (1961).

(12) A. I. Meyers and J. M. Greene, *J. Org. Chem.*, **31**, 556 (1966).

(13) A. I. Meyers and J. C. Sircar, *ibid.*, **32**, 4134 (1967).

(14) J. M. Greene, J. C. Getson, and A. I. Meyers, *J. Heterocycl. Chem.*, **1**, 300 (1964).

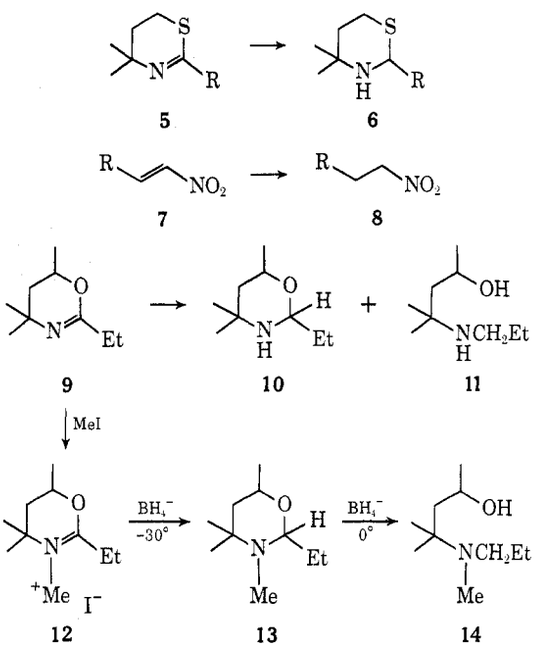
TABLE I

REDUCTION OF 9 AS A FUNCTION OF TEMPERATURE AND pH

Reaction[a] temp, °C	pH[b]	Moles $NaBH_4$[c]/ moles 9	% 10[d]	% 11[d]
0–5	5	1	53	47
0–5	7	1	77	23
0–5	9	1	87	13
−10	7	1	86	14
−20	7	1	91	9
−40	7	1	100	0

[a] Solvent used was THF–ethanol (1:1). [b] "pH" is purely apparent as measured by either pH meter or pH paper. Hydrochloric acid (6 *N*) was added as required. [c] Sodium borohydride was introduced as an aqueous solution. [d] Determined by vpc using Dow Silicone columns coated with 5% KOH.

it possible to effect quantitative conversion to the desired product. Furthermore, as the solution was changed during reduction from acidic (pH 5) to alkaline (pH 9) the amount of overreduction decreased. This, however, offered little in the way of a successful technique, since the degree to which the C=N link was reduced dropped off sharply. Since it was the intent of this program to maintain the mildest conditions possible for reduction, the pH was maintained at 7 and the temperature was lowered. In this fashion, the yield of reduction product was >98% and the amount of overreduced material (**11**) was negligible. For all practical



purposes, it was found that the reductions should be performed at −35 to −45°, although the pH range could vary from 5 to 8 without a significant increase in side products. In order to determine which of the two condition parameters was most critical and whether the overreduction to **11** is due to direct hydride attack on the tetrahydro-1,3-oxazine or hydride addition to the tautomeric imino form **2a**, the *N*-methyl oxazinium salt **12** was prepared. This was reduced to the *N*-methyltetrahydro-1,3-oxazine (**13**) at −30° in methanol. When the latter, now unable to exist in tautomeric forms owing to the absence of the NH function, was treated at pH 7 (0–5°), there was indeed obtained 26% of the open-chain amino alcohol **14**. When this experiment was repeated at −40°, no reaction oc-

TABLE II

2-SUBSTITUTED 4,4,6-TRIMETHYLTETRAHYDRO-1,3-OXAZINES (2)[a]

Registry no.	R	Yield,[b] %	Bp, °C (mm)	Analysis, found[c] C	H	N	2-H, δ[d]
36873-27-5	C_2H_5	57	68 (25)	68.66	12.23	8.68	4.1 (t)
36873-28-6	CH_2CO_2Et	78	82 (0.45)	61.44	9.93	6.60	4.6 (t)
36873-29-7	$CH_2CH_2NEt_2$	42	70 (0.20)	68.23	12.31	12.40	4.3 (t)
36873-30-0	CH_2Ph	88	92 (0.25)	76.82	9.80	6.55	4.4 (t)
31771-33-2	Ph	92	96 (0.30)[e]				5.2 (s)[f]
36873-32-2	*o*-Tolyl	89	94 (0.25)	76.52	9.42	6.44	5.2 (s)[f]
36873-33-3	2-Pyridyl	72	108 (0.30)	69.70	8.83	13.70	5.4 (s)

[a] Reductions performed using equimolar quantities of dihydro-1,3-oxazines and sodium borohydride at −35 and −40° in THF–EtOH. [b] Crude yields were higher; some cases resulted in considerable decomposition upon distillation. [c] Agrees within ±0.3% of calculated values. [d] Nmr spectra were taken on neat samples using TMS as internal standard. [e] Lit. bp 139–140° (15 mm): T. Urbanski, *et al.*, *Chem. Abstr.*, **51**, 1186 (1957); picrate, mp 166–167° (lit. mp 166–168°). [f] Proton integration was 0.68 owing to open-chain tautomer present.

curred. On the other hand, when **13** was treated with aqueous sodium borohydride at pH 3–5 at 0–5°, a 90% yield of **14** was obtained, while this reduction at −40° produced only 13% of the amino alcohol. From this study, it may be concluded that tetrahydro-1,3-oxazines are cleaved by direct hydride attack whose facility is temperature dependent. However, if the acidity is sufficiently high (pH 3–5), hydride attack is facile even at low (−40°) temperatures, presumably owing to the protonated tetrahydro-1,3-oxazine which behaves as a more reactive electrophile. Furthermore, the omnipresent imino form of tetrahydro-1,3-oxazines (**2a**) appears to be inert to hydride addition under the above described conditions (pH 7, −40°). A series of 2-substituted dihydro-1,3-oxazines (**1**) were subjected to the reduction conditions (−40°, pH 5–8) and the products **2** were readily isolated and characterized (Table II).

Cleavage of Tetrahydro-1,3-oxazines.—With an efficient and mild reduction method in hand, the tetrahydro-1,3-oxazines **2** were subjected to acidic cleavage in either 90% acetic acid or aqueous oxalic acid and the aldehydes **3** derived from these were isolated and characterized (Table III). In three cases, reductions were performed using sodium borodeuteride leading to C-1 deuterated aldehydes.

TABLE III

HYDROLYSIS OF TETRAHYDRO-1,3-OXAZINES **2** TO ALDEHYDES **3**

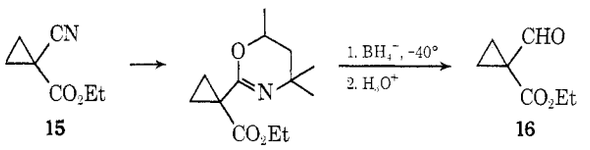
2, R =	Reaction condition[a]	Yield **3** 2,4-DNP, %	Mp, °C (lit.)
Et	A, 60 min, 90°	79	147–150 (148)[b]
	B, 90 min, 100°	74	
CH_2CO_2Et	A, 10 min, 90°	80	78–80 (158)[c]
	B, 60 min, 100°	*d*	
CH_2Ph	A, 5 min, 90°	78	118–120 (120)[e]
		77 (C-1D)[h]	
Ph	A, 5 min, 90°	77	240 (237)[b]
	B, 75 min, 100°	77 (C-1D)[h]	240
o-Tolyl	A, 24 hr, 25°	56[b]	95–100 (35 mm)[f]
2-Pyridyl	A, 5 min, 90°	57	227–229 (229)[g]
		62 (C-1D)[h]	

[a] A = 90% acetic acid, B = 3 *M* oxalic acid. [b] I. Heilbron, "Dictionary of Organic Compounds," Oxford University Press, London, 1965. [c] This compound is reported to melt at 158°: F. Bobery, *Justus Liebigs Ann. Chem.*, **683**, 132 (1965). The product obtained in this work gave correct elemental, mass, nmr, and ir analyses. [d] Free aldehyde was unstable and could not be obtained pure, except as 2,4-DNP derivative. [e] H. M. Fales, *J. Amer. Chem. Soc.*, **77**, 5118 (1955). [f] Isolated as pure aldehyde. [g] P. Grammaticakis, *Bull. Soc. Chim. Fr.*, 109 (1956). [h] Yield of C-1 deuterated aldehydes obtained by using sodium borodeuteride under identical reduction conditions.

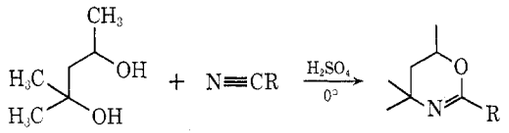
The most general method found for hydrolytic cleavage of the tetrahydro-1,3-oxazines was steam distillation from oxalic acid solution. In this fashion, pure aldehydes were consistently produced directly in the steam distillate, leaving the amino alcohol segment of the tetrahydro-1,3-oxazine in the distillation flask as the nonvolatile oxalate salt. For aldehydes which were insufficiently volatile to make steam distillation practical, reflux of the oxalic acid solution for 1–2 hr usually served the purpose, with the aldehyde being removed by extraction. It was found, in certain cases, that this method would result in decomposition of acid- or heat-sensitive aldehydes, and the aqueous acetic acid method at room temperature was then employed. Other means for releasing the aldehydes involved aqueous ethanolic ammonium chloride (6 *M*) or refluxing an ethanolic solution with hydroxylamine hydrochloride. The latter method, of course, converts the aldehyde directly to its oxime derivative. It is desirable to sample each of these techniques on a small scale to evaluate which proceeds with the best results. There were instances which failed to produce the aldehydic product owing to its sensitivity to acid (Table III, R = CH_2CO_2Et).

Synthesis of Dihydro-1,3-oxazines.—The next stage in the synthesis of aldehydes required that 2-substituted dihydro-1,3-oxazines be made readily available. A search of the literature revealed that most of the preparations involved the condensation of carboxylic acids,[15] nitriles,[16] or amides[17] with amino alcohols, olefins, or glycols in a cyclodehydrative or cycloaddition process. Since various methods are available for the direct reduction of nitriles, carboxylic acids, and related derivatives, there seemed to be no real advantage in converting these functional groups into dihydro-1,3-oxazines and ultimately to aldehydes. Recently,[18] however, this avenue provided the only approach for the conversion of the cyano ester **15** to the aldehyde **16**. It was decided to investigate the preparation of several 2-substituted oxazines and their potential for elaboration to a wide variety of structural features. The reaction[16] of simple nitriles with 2-

(15) Z. Eckstein and T. Urbanski, *Advan. Heterocycl. Chem.*, **2**, 311 (1963).
(16) E. J. Tillmanns and J. J. Ritter, *J. Org. Chem.*, **22**, 839 (1957).
(17) R. Schmidt, *Chem. Ber.*, **103**, 3242 (1970).
(18) R. V. Stevens, J. M. Fitzpatrick, M. Kaplan, and R. L. Zimmerman, *Chem. Commun.*, 857 (1971).



methyl-2,4-pentanediol (**17**) in concentrated sulfuric acid at 0° provided the most accessible precursors **18**–**21** for the aldehyde synthesis. All of these oxazines



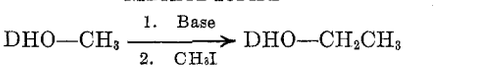
18, R = CH_3
19, R = CH_2Ph
20, R = CH_2CO_2Et
21, R = $CH{=}CH_2$

could be prepared or were available commercially in sufficient quantity to render them useful as starting materials (see Experimental Section).

If the process outlined in Scheme I could be successfully implemented with **18**, then similar reactions could be carried out on the oxazine **19** and **20** to produce α-phenyl and α-carboethoxy aldehydes, respectively. The 2-vinyl oxazine **21** contains a three-carbon unit which will be shown in later discussion to serve as a precursor to α,β-dialkylpropionaldehydes.

Alkylation Studies.—The 2-methyloxazine **18** was chosen as a candidate for elaboration as described in Scheme I. A search to find a suitable base that would produce a stable oxazine anion began with the usual repertoire available to the organic chemist. The results are tabulated in Table IV. Alkylation efficiency

TABLE IV
ALKYLATION OF 2,4,4,6-TETRAMETHYL-5,6-DIHYDRO-1,3-OXAZINE WITH METHYL IODIDE



Base[a]	Conditions[b]	DHO—CH_3, %	DHO—CH_2CH_3, %	Material[c] balance, %
NaH	THF, 25°, 24 hr	100	0	97
$NaCH_2SOCH_3$	DMSO, 20°, 24 hr	100	0	93
	DMSO, 70°, 24 hr	100	0	95
t-BuOK	THF, 25°, 24 hr	100	0	90
	THF, 5°, 24 hr	100	0	90
MeLi	THF, −60°, 4 hr	94	6	85
n-BuLi	THF, −20°, 2 hr	40	60	92
n-BuLi	THF, −60°, 2 hr	4	96	96
n-BuLi	Hexane, −60°	56	44	71
PhLi	THF, −60°, 2 hr	0	100	90
t-BuLi	THF, −60°, 2 hr	0	100	95
PhMgBr	Et_2O, 35°, 24 hr	100	0	93
MeMgI	Et_2O, 35°, 24 hr	100	0	90
	THF, 66°, 24 hr	100	0	94

[a] The ratio of base to oxazine was 1.1:1. [b] These are conditions employed only to generate the anion, after which methyl iodide was introduced (10% excess). Reactions were stirred for 15–18 hr at room temperature. [c] Products were analyzed by gas chromatography.

was followed by gas chromatography after addition of methyl iodide to the solutions. As seen from the data, the recovery of oxazines, alkylated or not, was quite good, indicating little decomposition during the experiments. Only *n*-butyl-, phenyl-, and *tert*-butyllithium were suitable as bases, whereas Grignard, alkoxide, hydride, and dimethylsulfinyl reagents failed. In addition, the temperature of the reaction was critical as seen by yields of alkylated oxazine at −20 and −60° using butyllithium. It should be noted that Table IV contains only a representative portion of the actual experiments performed in this study, and the results confirmed that an α-carbanion of dihydro-1,3-oxazines may indeed be efficiently prepared. For all practical purposes, the anion of the 2-methyloxazine was generated at −78° using 1.1 equiv of *n*-butyllithium and its formation was conveniently followed by the appearance of a bright yellow suspension. Upon addition of methyl iodide, the yellow suspension would, after several minutes, disappear, indicating that alkylation had occurred. This simple visual monitoring of the alkylation of oxazine carbanions would serve to indicate the reaction time for many different electrophiles to be described later.

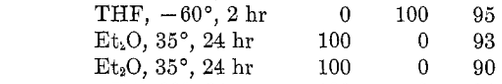
An evaluation of the relative rates of anion formation (THF, −78°) with organolithium reagents followed the series

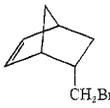
Base	*t*-BuLi	>	*n*-BuLi	>	PhLi
Time, min	5		50		85

with the appearance of the yellow anion suspension at the time indicated. With regard to solvents, the use of ether or hexane failed to produce complete anion formation even after 12 hr and therefore was precluded in this process.

The nature of the alkyl halide was also investigated to determine the limitations in structure and leaving group which would be encountered. The results are given in Table V. Alkyl chlorides (entry 1) gave very

TABLE V
EFFECT OF NATURE OF ELECTROPHILE ON ALKYLATION OF OXAZINE CARBANION (−78°, THF)

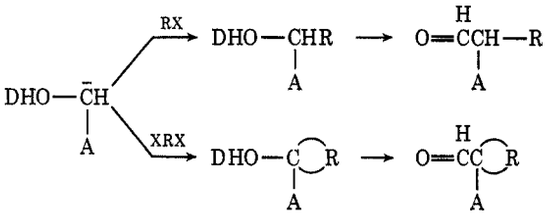


Entry	RX	DHO—CH_2R, %	DHO—CH_3, % recovered[a]
1	*n*-BuCl	6	88
2	*n*-BuBr	95	2
3	*n*-BuI	97	2
4	*n*-BuOTs	0	89
5	*i*-PrI	91	5
6	2-Bromopentane	12	80
7	2-Bromobutane	21	66
8	Bromocyclopentane	88	6
9	3-Bromocyclohexene	93	2
10	$CH_3CH_2C{\equiv}CCH_2CH_2Br$	3	95
11		0	93
12	$PhCH_2Cl$	98	2
13	$CH_2{=}CHCH_2Cl$	90	5
14	$CH_3CH_2C{\equiv}CCH_2Cl$	94	2

[a] Estimated by vpc or nmr to be ±2% of stated value. All reactions run by generating DHO—CH_2Li at −78°, followed by addition of 1.1 equiv of alkyl halide. After the mixture was allowed to warm to room temperature overnight, it was quenched in ice–water, extracted with ether, concentrated, and examined by nmr and vpc.

TABLE VI

ALDEHYDES FROM OXAZINE CARBANIONS AND ALKYL HALIDES AND DIHALIDES



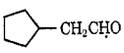
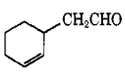
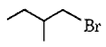
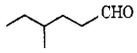
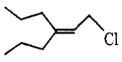
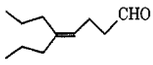
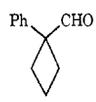
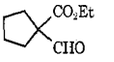
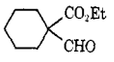
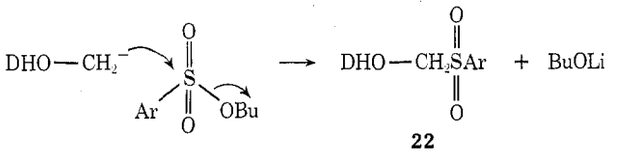
Entry	Alkyl halide	Registry no.	Aldehyde	Yield, %	Mp of 2,4-DNP, °C	Registry no.
			A = H			
1	CH_3I	123-38-6	CH_3CH_2CHO	60	149–150	725-00-8
2	n-C_3H_7I	110-62-3	$CH_3CH_2CH_2CH_2CHO$	65	102–104	2057-84-3
3	n-C_4H_9Br	66-25-1	$CH_3(CH_2)_4CHO$	65	102–103	1527-97-5
4	n-$C_3H_7CD_2Br$		$CH_3(CH_2)_3CD_2CHO$	*a*		
5	i-C_3H_7I	590-86-3	$(CH_3)_2CHCH_2CHO$	49	121–122	2256-01-1
6	CH_2=$CHCH_2Br$	2100-17-6	CH_2=$CH(CH_3)_2CHO$	51	116–118	1222-17-9
7	$CH_3CH_2OCH_2CH_2Br$	21744-96-7	$CH_3CH_2OCH_2CH_2CH_2CHO$	54	88–89	36873-54-8
8	$ClCH_2CH_2CH_2Br$	20074-80-0	$Cl(CH_2)_4CHO$	51	106–108	36873-55-9
9		5623-81-4		49	*b*	
10		19656-95-2		50	93–94	19656-96-3
11	$PhCH_2Br$	104-52-0	$PhCH_2CH_2CHO$	57	153–154	1237-68-9
12		32749-94-3		44	86–87	14093-70-0
13		34626-50-1		74	*b*	
14	$ClCH_2CH_2Br$	36873-36-6		69[d]	184–185	
15	$Br(CH_2)_3Br$	2987-17-9		20[c]	155–157	36873-59-3
16	$Br(CH_2)_4Br$	872-53-7		38[c]	153–154	20956-07-4
			A = Ph			
17	CH_3I	93-53-8	$Ph(CH_3)CHCHO$	65	133–134	5530-36-9
18	CH_3I (2.0 equiv)	3805-10-5	$Ph(CH_3)_2CCHO$	49	133–135	20401-28-9
19	n-C_3H_7Br	21765-78-6	PhCHCHO C_3H_7	64	122–123	36866-52-1
20	CH_2=$CHCH_2Br$	24036-43-9	PhCHCDO CH_2CH=CH_2	70[e]	100–103	24036-44-0
21	$Br(CH_2)_4Br$	29304-27-6	PhCHCHO $(CH_2)_4Br$	60	136–138	29304-28-7
22	$BrCH_2CH_2Br$	21744-88-7		57	186–188	36866-55-4
23	$Br(CH_2)_3Br$	1469-83-6		45[c]	154–156	1812-69-7
24	$Br(CH_2)_4Br$	21573-69-3		50	161–163	1812-68-6
			A = CO_2Et CO_2Et			
25	C_2H_5Br	36873-42-4	CH_3CH_2CHCHO	53	*b*	
26	C_3H_7Br	36873-43-5	$CH_3CH_2CH_2CHCHO$ CO_2Et	49	91–92	36866-58-7
27	n-C_4H_9Br	19361-66-1	$CH_3(CH_2)_3CHCHO$ CO_2Et	67	85–86	36866-59-8
28	CH_2=$CHCH_2Cl$	36873-45-7	CH_2=$CHCH_2CHCHO$	47	*b*	

TABLE VI (*Continued*)

Entry	Alkyl halide	Registry no.	Aldehyde	Yield, %	Mp of 2,4-DNP, %	Registry no.
29	CH_3I (2.0 equiv)	14002-65-4	$(CH_3)_2C(CO_2Et)CHO$	62	99–100	36866-60-1
30	$Br(CH_2)_4Br$	21744-91-2		68	134–135	21744-92-3
31	$Br(CH_2)_5Br$	36873-48-0		58	155–156	36866-62-3

[a] R. J. Liedtke and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6814 (1969). [b] Derivative not prepared, all spectral and elemental analyses consistent with correct structure. [c] Cycloalkyl dihydro-1,3-oxazine purified *via* bulb-to-bulb distillation prior to reduction step. [d] Isolated as 2,4-DNP derivative. [e] Reduction performed using sodium borodeuteride.

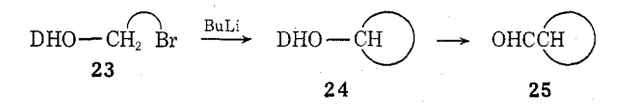
poor yields, whereas the corresponding bromides and iodides reacted efficiently (entries 2, 3). Tosylates (and mesylates), entry 4, were virtually inactive toward displacement by the oxazine carbanion, producing only the recovered oxazine and a 10% yield of the sulfone **22**. The latter undoubtedly arises from nucleophilic



22

displacement on sulfur rather than carbon. Organolithium reagents have been reported[19] to displace tosylates only in ether solvent and fail to accomplish this transformation in tetrahydrofuran. Unfortunately, the oxazine carbanion cannot be prepared in good yields in ether solvent. Secondary halides of increasing steric bulk (entries 5, 6, 7) led to progressively poorer yields of alkylation and higher yields of elimination. On the other hand, secondary halides derived from alicyclic systems, where the steric bulk is reduced, afford good yields of alkylated product (entries 8, 9). A further limitation was observed when homopropargyl (or homallylic) halides were investigated. The result was essentially complete recovery of oxazine by virtue of extensive elimination to the conjugated ene–yne (or diene) systems (entry 10). Thus, the acidity of the propargylic (or allylic) proton competes favorably with halide substitution, rendering alkylation unsatisfactory when this structural feature is present. The *endo*-bromomethylnorbornene (entry 11), owing to the limited accessibility to the electrophilic site, also failed to alkylate the oxazine carbanion. Activated chlorides (entries 12, 13, 14) behaved normally and led to good yields of alkylated oxazines. It should be noted here that *in no instance was there observed N-alkylation of the oxazine or polyalkylation of the 2-methyl group.*

The lack of polyalkylation was indeed a surprising result in light of the fact that the 2-methyloxazine **18** contains two remaining α hydrogens which should be capable of further reaction with either butyllithium or the lithio oxazine. The fact that intramolecular cyclization of 2-(ω-bromoalkyl)oxazines (**23**) was effected by butyllithium to the cycloalkyl derivatives **24** and ultimately to cycloalkanecarboxaldehyde (Table VI, entries 14–16) further contributed to the inconsistent behavior of 2-alkyloxazines. A systematic study of primary, secondary, and tertiary carbanions derived from 2-alkyloxazines was undertaken and led to the understanding of this behavior. The 2-methyl (**18**), 2-ethyl (**18a**), and the 2-isopropyl oxazines (**18b**) were examined since these are all capable of producing a primary, secondary, and tertiary carbanion, respectively.

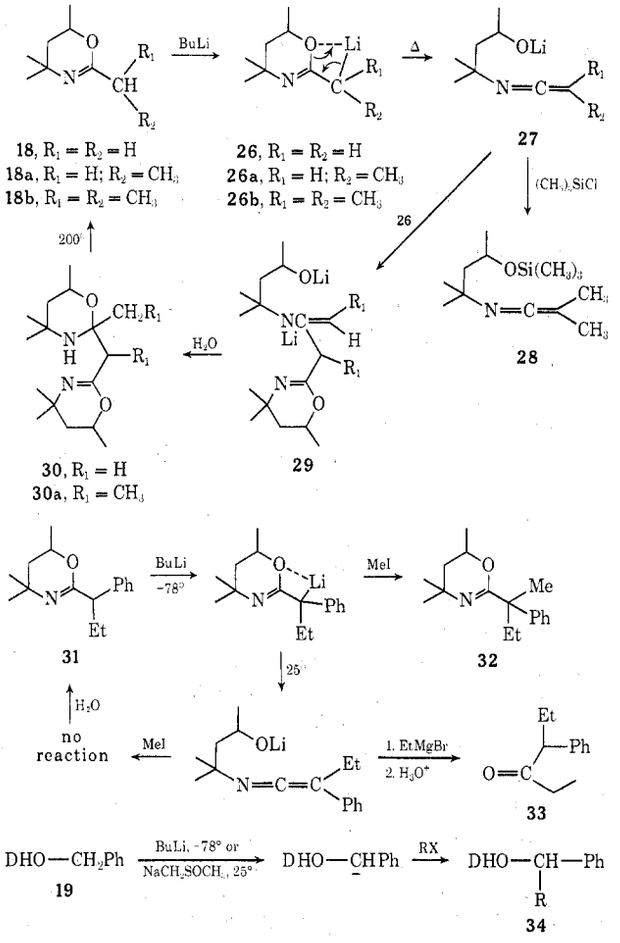


23 **24** **25**

The lithio oxazine **26** was formed in the usual manner (butyllithium, −78°, THF) and allowed to warm to room temperature in the absence of an external electrophile. Upon quenching in water, the product, isolated in 84% yield, was the dimeric oxazine **30**. Thus, it appears that the primary carbanion which is stable and capable of alkylation at −78° slowly rearranges, as the temperature rises, to the ketenimine **27** ($R_1 = R_2 =$ H) and is alkylated by unrearranged carbanion producing the adduct **29** ($R_1 =$ H). Hydrolysis leads to the dimer **30**, which arises from cyclization of the initially formed hydroxy imine. The bicyclic dimer **30** is temperature sensitive and upon heating (~190°) or injecting into a vpc instrument whose injection port is heated to 200°, a facile reversal occurs and the 2-methyloxazine **18** is recovered quantitatively. In the case of **18a**, no secondary carbanion **26a** was formed when treated with butyllithium at −78 to −50° as evidenced by the lack of methylation (methyl iodide) or deuteration (D_2O). When a solution containing the 2-ethyloxazine and 1.0 equiv of butyllithium was allowed to warm from −50° to room temperature with or without methyl iodide present, the yield of 2-isopropyloxazine (**18b**) was less than 10% while the dimer **30a** was isolated in 88% yield. The latter could be obtained pure by distillation below 120°, a temperature insufficient to cause reversal to the monomeric oxazine **18a**. A small volatile forerun in this distillation was also trapped in a Dry Ice collector and characterized only through its infrared spectrum, which indicated C=C=N (2060 cm^{-1}) and OH (3550 cm^{-1}) absorption. This product was presumably **27** (Li = H, $R_1 =$ H, $R_2 = CH_3$) formed by hydrolysis of the *O*-lithio salt during aqueous work-up. This behavior is consistent with the lower acidity of the α proton in the 2-ethyloxazine, which is removed only after the temperature rises in the range −50 to 25° and rearrangement of **26a** ($R_1 =$ H, $R_2 = CH_3$) to the ketenimine **27** occurs. Since this secondary carbanion forms at a temperature to which it is unstable,

(19) W. D. Korte and L. Kinner, *Tetrahedron Lett.*, 603 (1970).

rearrangement ensues and alkylation by electrophiles cannot compete meaningfully. Turning to the 2-isopropyloxazine **18b** as a precursor to a tertiary carbanion, no proton abstraction takes place with butyllithium in THF from −78 to 0°. This was determined by lack of deuteration or the absence of any dimeric products. However, when **18b** in THF containing butyllithium was allowed to stand at room temperature, followed by the addition of trimethylchlorosilane, a 35% yield of the ketenimine trimethylsilyl ether **28** was isolated. The remainder of the material was addition product between the ketenimine and *n*-butyllithium acting as a nucleophile. This latter process has formed the basis for a useful ketone synthesis which will be described in detail in a future paper.[20] The ketenimine was prepared in good yield (77%) by using lithium diisopropylamide in place of butyllithium as the base to remove the tertiary proton. The reason for this improved yield is the fact that the diisopropyl amide, although serving as a good base, is too bulky to add to the ketenimine once formed. The lack of dimer from **18b** as well as the high yield of ketenimine **28** is



consistent with the fact that the tertiary carbanion **26b** is formed at a temperature (0–20°), which virtually forbids its existence, and rearrangement is sufficiently rapid that no opportunity for dimer formation is present.

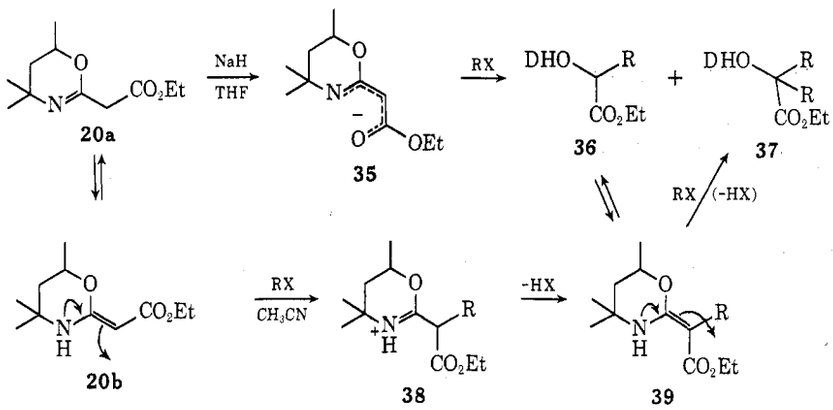
This oxazine–ketenimine rearrangement was further studied using a system (**31**) which was deemed suitable for observing both the carbanion and the ketenimine intermediates. By treating **31** with butyllithium at −78° it was shown that the α proton can be removed owing to the delocalization of the anion by the adjacent phenyl group. Addition of methyl iodide at −78° led to the α-methyloxazine **32** in 95% yield. However, if the lithio oxazine was allowed to warm to room temperature and then treated with methyl iodide, the product obtained after aqueous work-up was only the starting oxazine **31**. On the other hand, if ethylmagnesium bromide was added to the lithio oxazine at room temperature and then quenched with water, the ketone **33** was isolated in good yield. The presence of the ketone confirmed that the lithio oxazine had rearranged to the ketenimine on warming to room temperature and had been alkylated by the Grignard reagent. The resulting adduct would then be a typical enamine which is expected to produce the ketone in aqueous medium.[20]

The alkylation of 2-benzyl dihydro-1,3-oxazine (**19**) was found to proceed *via* its carbanion to α-alkyl-α-phenyl oxazines (**34**) in high yield. The carbanion could be formed in this case using either butyllithium (−78°, THF) or the methylsulfinyl carbanion (DMSO, 25°) developed by Corey.[21] Furthermore, as seen from Table IV, the 2-methyloxazine was inert to prolonged contact with Grignard reagents; yet this was not the case with the 2-benzyloxazine. Owing to the increased acidity of the benzyl protons, Grignard reagents were found, after lengthy exposure (25°, 24 hr), to abstract the α proton of **19** (determined by deuteration). This behavior was not observed (Table IV) when the oxazine bears only a 2-alkyl substituent and will be shown later to provide a useful method for performing Grignard reactions in the presence of the oxazine ring.

Turning now to the 2-carboethoxy dihydro-1,3-oxazine (**20**) and its potential for elaboration, it was seen early in the study by ir and nmr that it existed in two tautomeric forms, **20a** and **20b**. The α protons in **20a** are readily exchanged with deuterium oxide and the anion **35** could be routinely prepared by the usual alkoxides in alcohol. The use of the nonnucleophilic bases, sodium hydride or potassium *tert*-butoxide, was found to be preferable, since ethoxide ion slowly caused ring rupture of the oxazine ring. When **35** was formed in THF, DMSO, or HMPA and treated with benzyl bromide, a mixture of mono- and dialkylated oxazines, **36** and **37**, was formed. The dialkylated product could be formed in high yield by utilizing 2.0 equiv of base; however, all attempts to prepare only the monoalkylated product **36** (R = benzyl) met with little success. It was further found that the mono- and dialkylated oxazine could also be formed by merely heating a solution of **20** with benzyl bromide in acetonitrile, thus confirming the enamine characteristics of the carboethoxy oxazine. However, when **20** was heated with an unactivated bromide (*n*-butyl bromide) in acetonitrile, only the monoalkylated product **38** and starting material **20** were recovered in a 1:1 mixture. It thus became obvious that the enamine **39** was incapable of being alkylated by simple alkyl bromides, even at reflux temperatures of acetonitrile. This parallels the behavior of simple enamines, which also give poor yields of alkylation products with unactivated

(20) Preliminary results have been reported: A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *J. Amer. Chem. Soc.*, **93**, 2314 (1971).

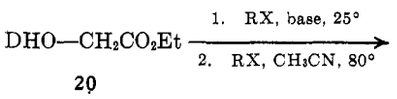
(21) E. J. Corey and M. Chaykovsky, *ibid.*, **84**, 867 (1962).



halides, whereas good yields are obtained with highly electrophilic halides.[22] The process was then reexamined using unactivated alkyl bromides on the anion **35**. The results are given in Table VII. In all cases good yields of the monoalkylated oxazine **36** were produced when the anion was treated at room temperature with primary or secondary alkyl halides. A technique for synthesis of either mono- or dialkylated carboethoxy oxazines was now in hand.

TABLE VII

ALKYLATION OF THE 2-CARBOETHOXYMETHYL OXAZINE **20** WITH ALKYL HALIDES



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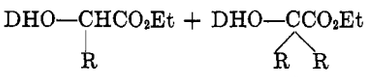


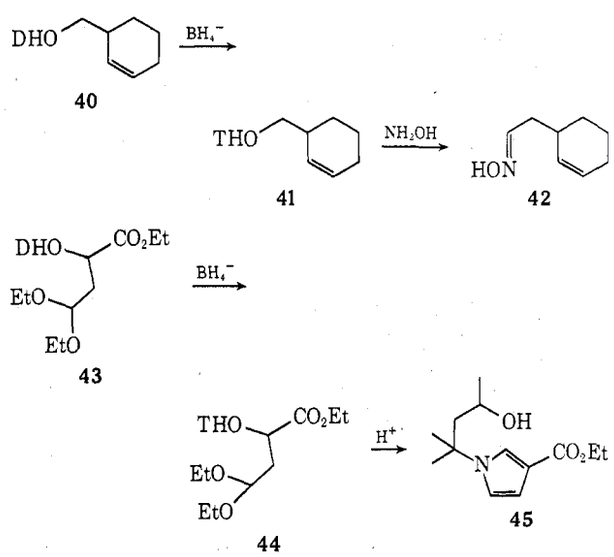
36 **37**

RX	Alkylation method[a]	**20**,[b] %	**36**,[b] %	**37**,[b] %
Ethyl bromide	A	2	96	2
	B	47	53	
n-Propyl bromide	A	3	94	2
	B	40	60	0
n-Propyl iodide	B	29	67	4
n-Butyl bromide	A	2	94	4
	B	50	50	0
Benzyl bromide	B	10	50	40
Benzyl chloride	B	13	73	12
2-Bromohexane	A	20	75	0
$BrCH_2CH(OEt)_2$	A	20	80	0

[a] Method A—The anion of **20** was formed using 1.1 equiv of potassium *tert*-butoxide or sodium hydride in THF or DMSO. Reactions, after addition of the alkyl halide, were allowed to stir for 18 hr at room temperature. Method B—Equimolar quantities of **20** and alkyl halide were heated in anhydrous acetonitrile for 24–48 hr, the solvent was evaporated, and the residue was neutralized with 10% sodium bicarbonate, extracted with ether and concentrated. [b] Determined by gas chromatographic analysis.

With the alkylation, reduction, and cleavage of the oxazines **18**–**20** demonstrated to be a feasible sequence, the synthetic utility of this method was investigated to determine its scope for the preparation of a variety of aldehydes.

Synthesis of Aldehydes. Substituted Acetaldehydes.—The carbanions derived from dihydro-1,3-oxazines **18**–**20** were subjected to alkylation with various alkyl halides and dihalides, reduced with sodium borohydride or deuteride, and hydrolyzed to the corresponding aldehydes (Table VI). Since several aldehydes were obtained directly as the 2,4-DNP derivatives (entry 14), it was of interest to determine if aldehydes could be isolated as other derivatives. When the cyclohexenyl oxazine **40** was reduced to the tetrahydro-1,3-oxazine **41** and treated with hydroxylamine hydrochloride in boiling ethanol, a good yield of the oxime **42** was obtained. The ester oxazine **43**, which was smoothly reduced to the tetrahydro derivative **44**, underwent pyrrole formation to **45** rather than the expected cleavage to the dialdehyde.[23] A recent report[24] described the conversion of the tetrahydro-1,3-oxazine **46** to the nitrone **47** which proceeded directly in an *in situ* intramolecular 1,3-dipolar addition to the isoxazolidine. The ability to reduce an acetylenic linkage in the presence of the oxazine ring was demonstrated by the transformation of **49** to the cis olefin without effect upon the oxazine moiety. Reduction and hydrolysis of the oxazine ring led to the cis aldehyde **50** in 54% overall yield.[25]



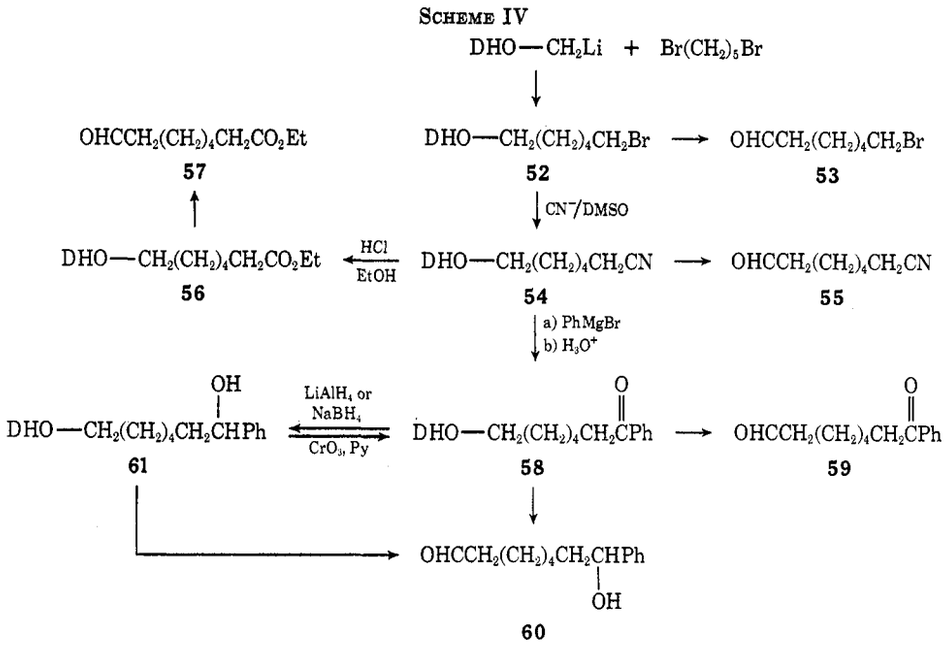
(22) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovic, and R. Terrell, *J. Amer. Chem Soc.*, **85**, 207 (1963).

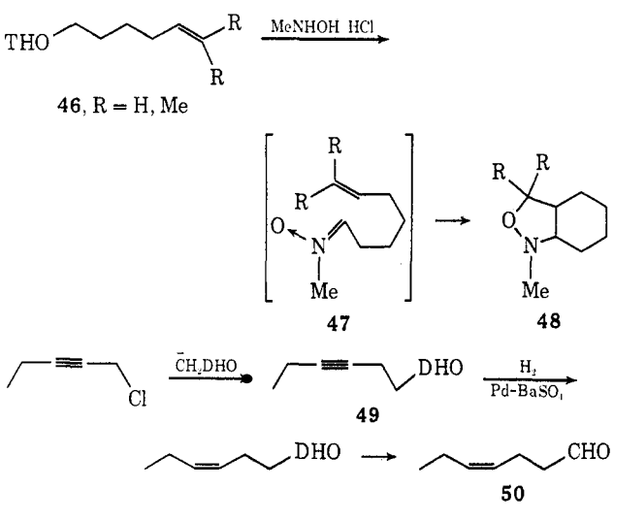
(23) A. I. Meyers, T. A. Narwid, and E. W. Collington, *J. Heterocycl. Chem.*, **8**, 875 (1971).

(24) N. A. LeBel and E. G. Banucci, *J. Org. Chem.*, **36**, 2440 (1971).

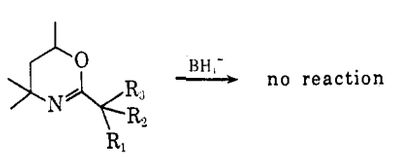
(25) Olefin linkages present on the side chain of dihydro-1,3-oxazines may also be saturated (PtO_2, EtOH, 25°, 30 min) without any effect upon the heterocycle. We thank Dr. Harvey Taylor of these laboratories for these experiments.

SCHEME IV





The major limitation to the aldehyde synthesis is found when the α carbon of the oxazine was completely substituted (**51**). Thus, when three alkyl



51 ($R_1 = R_2 = R_3 >$ CH_3 or Aryl)

groups (except methyl) were present, the borohydride reduction failed to reduce the C=N link. This is an obvious steric effect which prohibits hydride addition when a bulky quaternary carbon is present. This limitation is not encountered when two of the substituents are part of a cyclic moiety (Table VI, entries 22–24, 30, 31) or when two of the groups are methyl (entries 18, 29). There is an advantage to this finding in that the cases where polyalkylation is possible (*i.e.*, **20**) producing mono- and dialkylated oxazines **36** and **37**, respectively (Table VII), only the former will reduce to the tetrahydro oxazine. The aldehyde thus produced is free from the dialkylated isomer, since the dihydro oxazine **20** does not form any interfering products (Table VI, entries 25–28) upon oxalic acid hydrolysis.

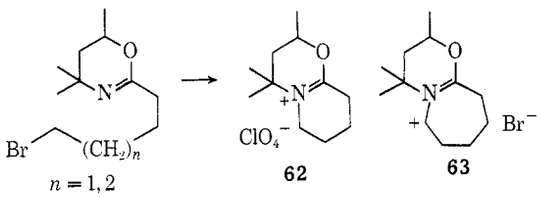
The incorporation of functionality into the aldehydes prepared by the oxazine route was further investigated using the ω-bromohexyl oxazine **52** formed from the carbanion (CH_2DHO) and 1,5-dibromopentane. The bromohexyl oxazine could be prepared and utilized without purification for subsequent transformations. It was found, however, preferable in some cases to isolate **52** in pure form (70–80%). This compound was chosen as a typical substrate for which a variety of reactions could be evaluated (Scheme IV). As expected, the bromohexyl oxazine was routinely converted to 7-bromoheptaldehyde **53** by the borohydride–oxalic acid sequence. Reaction of **52** with sodium cyanide in dimethyl sulfoxide[26] at 55° furnished the cyanohexyl oxazine **54** in excellent yield. The latter was also found to be a suitable precursor to 7-cyanoheptaldehyde (**55**). Treatment of the cyanohexyl oxazine with ethanolic hydrogen chloride cleanly produced the ester oxazine **56** and this was transformed into the ester aldehyde **57** in the usual fashion.

Since the metalation study mentioned earlier (Table IV) indicated no reaction of the oxazines under prolonged contact with Grignard reagents, the cyanohexyl oxazine **54** was treated with phenylmagnesium bromide and afforded the keto oxazine **58** without interference by the oxazine ring. The borohydride reduction at −45° could be controlled with the quantity of reducing agent to give either the keto aldehyde **59** or the hydroxy aldehyde **60** after oxalic acid cleavage. Of additional interest is the fact that *the keto oxazine* **58** *was reduced to the hydroxy oxazine* **61** *by sodium borohydride in ethanol–water (pH 11) at 0–25° without reducing the C=N link.*[27] The unusual stability of the dihydro-1,3-oxazine ring system was further revealed

(26) L. Friedman and H. Schechter, *J. Org. Chem.*, **25**, 877 (1960). The crude 6-bromohexyloxazine **38**, formed in 90% yield, could also be transformed into the nitrile **40**, and the latter purified by distillation. This gave somewhat higher yields of nitrile.

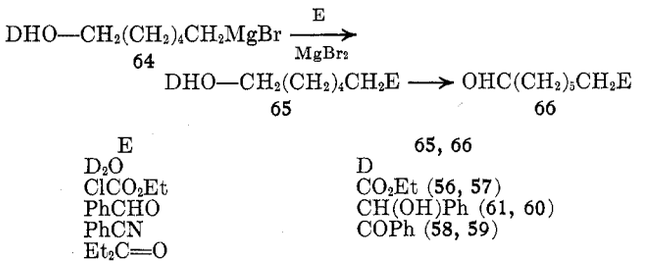
(27) It was also observed that lithium aluminum hydride will not attack the dihydro-1,3-oxazine ring at room temperature for 16 hr. In this fashion, **58** was reduced to **61** in ether or THF.

by its inertness to oxidizing agents and the absence of amine oxide formation during the transformation of the hydroxy oxazine **61** to the ketone **58**. The outline described by Scheme IV serves to illustrate the versatility of bromoalkyl oxazines and the ability of the heterocyclic ring to withstand a variety of reaction conditions. A similar sequence was performed using the related bromopentyl and bromobutyl oxazines. However, there was considerable production of the cyclic oxazinium salts **62** and **63**, which were isolated



as the stable perchlorate and bromide, respectively. This facile ring closure was mainly responsible for the low yield of cyclobutanecarboxaldehyde (entry 15, Table VI). The preparation of the corresponding chlorobutyl and chloropentyl oxazines took place without undue difficulty. The former was sufficiently stable to be utilized as the precursor to 5-chlorovaleraldehyde (entry 8, Table VI). Presumably, the reactions surveyed in Scheme IV could be applied to the chlorobutyl and chloropentyl oxazines, although this was not pursued.

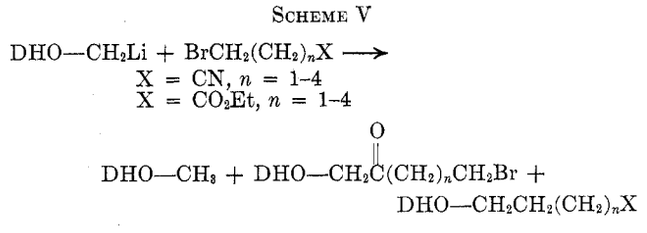
The inertness of the oxazines toward Grignard reagents was further demonstrated by the ready formation of the Grignard reagent **64** from the 6-bromomethyloxazine **52**. The reagent could be formed in ether or tetrahydrofuran, although it is sparingly soluble in the former solvent. A series of electrophiles, E, was examined with varying degrees of success. Addition of deuterium oxide to **64** led to the 6-deuteriohexyloxazine **65** (E = D) in over 92% yield and ultimately to the deuterated aldehyde **66** (E = D) in 52% overall yield. Surprisingly, the oxazine Grignard failed to react to any appreciable extent with benzaldehyde, benzonitrile, 3-pentanone, or ethyl chloroformate; in each instance the 2-hexyloxazine **65** (E = H) was recovered in high yield. Relying on the assumption that the lone electron pairs present on oxygen and nitrogen were complexing with the magnesium (intra- or intermolecularly) the reactions were repeated using magnesium bromide. The purpose of the salt was twofold: (a) to complex with either oxygen and nitrogen, thus releasing the Grignard complex, and (b) to enhance the electrophilic nature of the electrophiles. Indeed, when an ethereal solution of the 6-bromohexyloxazine was treated with magnesium metal containing 1 equiv of magnesium bromide (prepared from ethylene dibromide and magnesium), there was no precipitation of the Grignard reagent, but a two-phase solution. Addition of benzaldehyde led to the normal addition product **65** (E = HCOHPh) in 65% yield. The structure was proved by simple comparison to **61** prepared earlier by the route in Scheme IV. Reaction of the Grignard **64** in the presence of magnesium bromide with ethyl chloroformate or benzonitrile furnished the oxazine **65** (E = CO_2Et and COPh, respectively). These were likewise identified by comparison with the oxazines **56** and **58** prepared from the cyano-



hexyl oxazine **54**. It should be noted here that these reactions were less efficient (35–50%) than those produced from the cyanohexyl oxazine, and the latter is considered to be a more advantageous route. When the Grignard **64** was treated with 3-pentanone with or without magnesium bromide present, no reaction occurred. It is therefore concluded that the oxazine Grignard reagent **64** is lacking in its nucleophilic reactivity, owing perhaps to considerable complexation, solubility (two-phase liquid system), and the length of the hydrocarbon chain. The latter feature has been noted to reduce reactivity of Grignard reagents.[28]

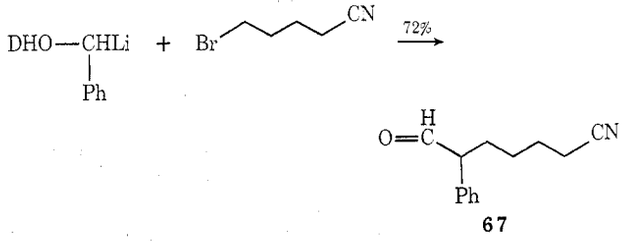
The successful implementation of functional group incorporation into 2-substituted dihydro-1,3-oxazine (*i.e.*, **52**) took on an added importance when it was learned that the oxazine carbanion lacked specificity in reaction with functionalized halides (Scheme V).

SCHEME V



Thus, addition of bromo esters or nitriles of varying chain lengths led to products from proton abstraction, displacement of halides, and addition to the unsaturated sites.

In contrast to the results in Scheme V, the anion derived from the benzyl oxazine reacted cleanly with 5-bromovaleronitrile, displacing bromide ion only. Sequential borohydride reduction and hydrolysis produced the cyano aldehyde **67** in good overall yield.



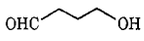
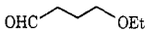
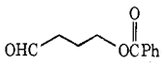
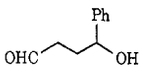
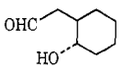
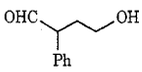
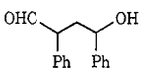
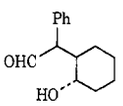
The benzyl carbanion, owing to its enhanced delocalization by the phenyl group, is significantly less reactive and therefore more selective.

Reactions of α,ω-dihalides with 2.0 equiv of the oxazine carbanions led to double halide displacements and utilimately to α,ω-dialdehydes (Scheme VI). The

(28) Long-chain Grignard reagents have been shown to react with less efficiency than their more compact counterparts (Kharash and Reinmuth, "Grignard Reaction of Non-Metallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954).

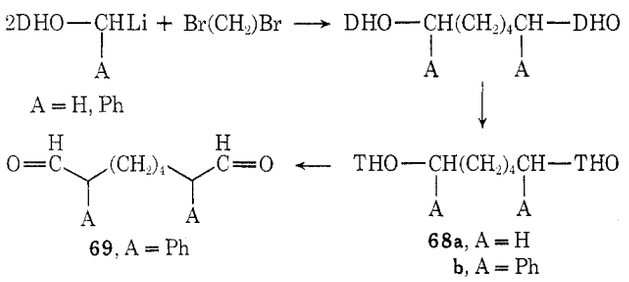
TABLE VIII

γ-HYDROXY ALDEHYDES AND OXO DERIVATIVES FROM DIHYDRO-1,3-OXAZINES

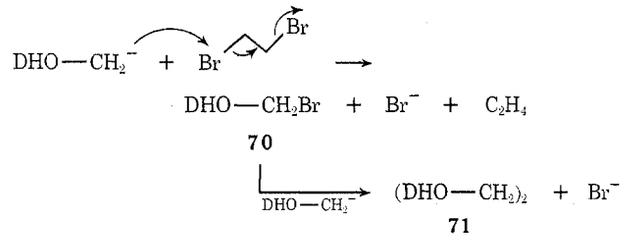
Oxazines	Epoxide	Additional electrophile	Aldehyde[i,j]	Registry no.	Yield, %
DHO—CH_3	Ethylene			1708-33-4	64[a]
DHO—CH_3	Ethylene	Ethyl iodide			59[b]
DHO—CH_3	Ethylene	Benzoyl chloride		22927-31-7 (23107-26-8)	67[c]
DHO—CH_3	Styrene			36866-66-7 (22927-20-4)	68[d]
DHO—CH_3	Cyclohexene			36871-99-5 (23099-01-6)	57[e]
DHO—CH_2Ph	Ethylene			36866-68-9 (22927-21-5)	69[f]
DHO—CH_2Ph	Styrene			36866-70-3 (22927-22-6)	65[g]
DHO—CH_2Ph	Cyclohexene			36872-01-2 (22985-63-3)	60[h]

[a] Owing to high aqueous solubility, product was isolated as 2,4-DNP, mp 116–118°. [b] 2,4-DNP, mp 88–89°. [c] 2,4-DNP, mp 103–105°. [d] 2,4-DNP, mp 106–107°. [e] 2,4-DNP, mp 78–79°. [f] 2,4-DNP, mp 99–101°. [g] 2,4-DNP, mp 146–147°. [h] 2,4-DNP, mp 174–175°. [i] All hydroxy aldehydes existed predominantly as their cyclic acetals. [j] Registry numbers for 2,4-DNP derivatives are given in parentheses.

SCHEME VI



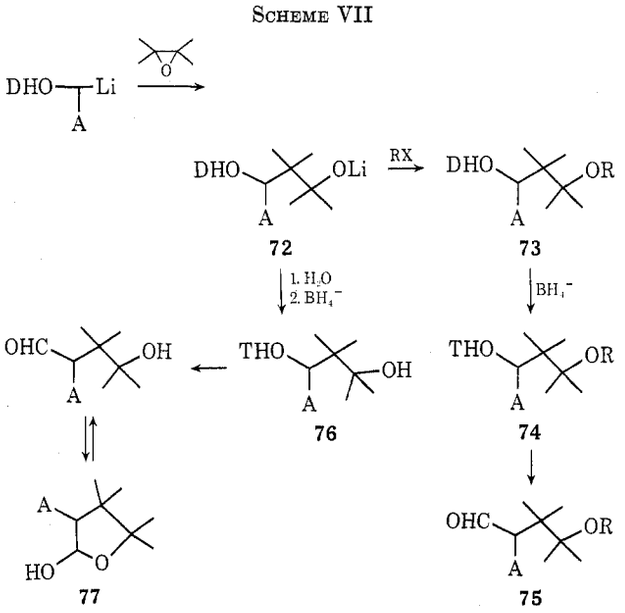
preparation of 2,7-diphenyl-1,8-octanediol (**69**) is exemplary of this approach. The unstable nature of simple α,ω-dialdehydes to oxalic acid solution and their high solubility in aqueous media precluded their efficient isolation from the cleavage of bistetrahydro-1,3-oxazines, **68a**. Nevertheless, the latter derivatives may be purified and stored in their "protected" form for subsequent use. The simplest dialdehyde prepared *via* this method was the tetrahydro-1,3-oxazine derivative of succindialdehyde. This was formed by addition of ethylene bromide to the oxazine carbanion which gave, *in situ*, the bromomethyl derivative **70** followed by rapid displacement with unreacted carbanion to the bisoxazine **71**. Reduction with sodium borohydride



led to the masked succindialdehyde. When 1-chloro-2-bromoethane was used in place of ethylene bromide, alkylation proceeded normally to the chloropropyl derivative (Table VI, entry 14).

Epoxides also served as useful electrophiles, alkylating the oxazine carbanions in good yield (Scheme VII).

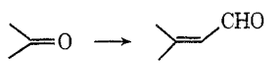
SCHEME VII



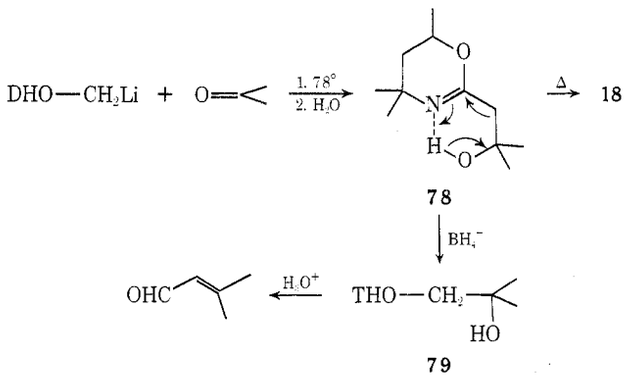
The usual borohydride hydrolysis sequence furnished γ-hydroxy aldehydes (Table VIII). The initially formed alkoxides **72** were treated as their lithio salts *in situ* with several typical electrophiles (ethyl iodide, benzoyl chloride) at room temperature in THF solution in anticipation of preparing **73**. However, no

significant amount of alkylation occurred. The highly covalent oxygen–lithium bond in **72** is undoubtedly a poor nucleophile,[29] this prohibiting any further alkylation. Nevertheless, the hydroxypropyl oxazines **73** (R = H) were conveniently alkylated by treatment with sodium hydride to form the sodium alkoxide **73** (R = Na) followed by the addition of an electrophile (Table VIII). In this fashion, after reduction to the tetrahydro oxazine **74**, the oxo derivatives **75** of the γ-hydroxy aldehydes were obtained. Similarly, borohydride reduction of crude oxazines **72** produced the tetrahydro derivatives **76** and ultimately the hydroxy aldehydes **77**, which existed predominantly in their hemiacetal forms. This approach to γ-oxygenated aldehydes represents a distinct improvement over previous methods, which require oxidative cleavage of 4-alken-1-ols and are only sparsely described in the literature.[30]

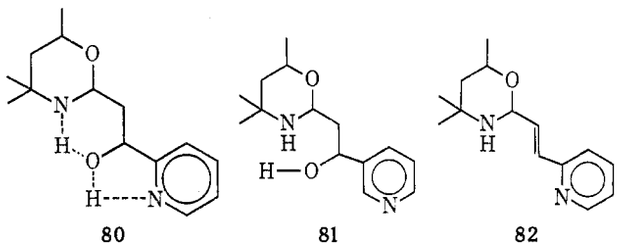
α,β-Unsaturated Aldehydes.—The utilization of carbonyl components as electrophiles to effect a two-carbon homologation to α,β-unsaturated aldehydes has been reported using lithio imines,[31] imino phosphoranes,[32] acetaldehyde ylides,[33] and more recently 1,3-bis(thiomethyl)allyl anions.[34]



The reaction of lithio oxazines with a variety of carbonyl compounds produced at −78° the adducts **78** after quenching. Early attempts to purify these adducts by distillation resulted in facile thermal retrocondensation to starting materials. This is not unexpected owing to the built-in basic site and the well-known retro condensation of "aldol-type" products under the influence of base and heat. Fortunately, purification of **78** is not a necessary prerequisite to the success of the overall sequence and this step is readily circumvented by reduction of crude **78** to the tetrahydro-1,3-oxazine, **79**. The strong hydrogen bonding in **78** and **79** is readily seen by the infrared absorption



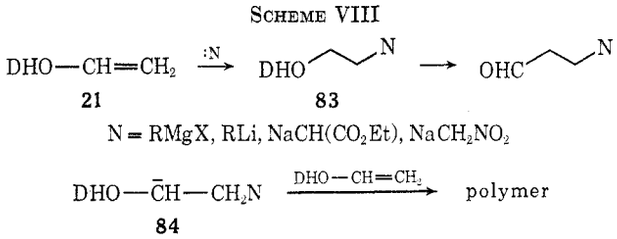
(3350–3200 cm^{-1}), and this property is manifested in the rapid movement of these compounds on tlc. Hydrolytic cleavage of **79** in oxalic acid solution provides the α,β-unsaturated aldehydes (Table IX). The pronounced stability of certain hydrogen-bonded tetrahydro-1,3-oxazines (*e.g.*, **80**), derived from 2-pyridinecarboxaldehyde, precluded its use as a route to 2-pyridyl-2-acrolein.[35] The latter could not be cleaved under a variety of acidic conditions, although the 3- (and 4-) pyridine derivatives **81** behaved in the expected manner (Table IX, entry 24, 25). Attempts to disrupt the hydrogen bonding by conversion to the olefin **82** were fruitless.[36] In certain instances, the unsaturated aldehydes obtained from the acidic cleavage were mixtures containing the β,γ isomers (entries 3, 5, 6, 7) which reflected their relative thermodynamic stabilities.



80 **81** **82**

α-Alkyl Aldehydes.—The utility of the 2-vinyldihydro-1,3-oxazine **21**, as a potential source of β-substituted propionaldehydes (Scheme VIII) by virtue of a

SCHEME VIII



Michael-type addition of various nucleophiles, was investigated. When Grignard or organolithium reagents were added to **21** in THF, ether, or pentane in the temperature range −78 to 25°, only polymeric material was obtained. On the other hand, the use of sodiomalonic ester in ethanol produced the Michael adduct **83** [N=CH(CO$_2$Et)$_2$] in excellent yield. It therefore appears that the initially formed secondary anion **84** is highly unstable (as in **26a**) and proceeds, in the presence of vinyl functions, on to polymer. In the presence of a protic solvent, however, the anion is rapidly intercepted and the reaction produces the expected product.

In order to circumvent this problem, it was decided to introduce an electrophilic trapping agent (methyl iodide) prior to addition of the organometallic in anticipation that the carbanion **84** would be efficiently alkylated, thus intercepting the polymerization process. Indeed, this experimental modification proved to be a desirable one. The addition of phenylmagnesium bromide to a THF solution containing **21** and 1.1–1.5 equiv of methyl iodide resulted in a 85–90% yield of dialkylated oxazine **85** (R = Ph). Repeating the reaction with phenyllithium, on the other hand, still resulted in extensive polymerization. This may be

(29) W. E. Truce and L. W. Christensen, *J. Org. Chem.*, **36**, 2538 (1971).
(30) R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, 197 (1948); B. Helfrich and O. Lecher, *Chem. Ber.*, **54**, 930 (1921).
(31) G. Wittig and H. Reiff, *Angew. Chem., Int. Ed. Engl.*, **7**, 7 (1968).
(32) W. Nagata and Y. Hayase, *Tetrahedron Lett.*, 4359 (1968).
(33) For a review of this subject *cf.* A. W. Johnson, "Ylid Chemistry," Academic Press, New York, N. Y., 1966, pp 152, 205.
(34) E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971).
(35) Table IX, ref *f*.
(36) A recent modification of this synthesis using the Wittig reagent of dihydro-1,3-oxazines, DHO—CH=PPh$_3$, has been shown to give the corresponding olefins with carbonyl compounds. This technique now allows the formation of certain α,β-unsaturated aldehydes by omitting the hydroxy adduct (G. R. Malone, Ph.D. Thesis, Wayne State University, 1972).

TABLE IX
FORMATION OF α,β-UNSATURATED ALDEHYDES FROM DIHYDRO-1,3-OXAZINES

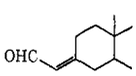
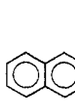
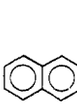
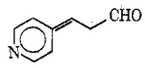
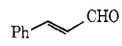
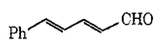
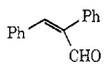
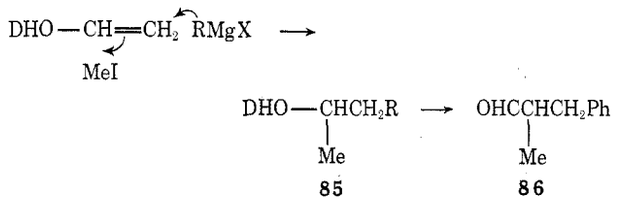
Entry	Carbonyl component	α,β-Unsaturated aldehydes	Registry no.	Overall yield, %	2,4-DNP, mp, °C	Registry no.
1			107-86-8	50	221–222[g]	6106-53-2
2			21849-62-7	62	169–170[g]	36866-89-4
3		 (+ 10% β,γ)	34626-45-4	73		
4			5623-82-5	63	179–180	7014-77-9
5		 (+ 15% β,γ)	1713-63-9	53	193–195[g]	1713-65-1
6	3-Cholestanone	 (+ 15% β,γ)	36866-76-9	69	110–112	36866-92-9
7			36872-03-4 (cis) 26532-25-3 (trans) 36866-77-0 (endo)	61[a]		
8			1210-39-5	60	197–198	5109-19-3
9			21878-52-4 (cis) 21866-70-6 (trans)	49[b]	200–202	3491-79-0
10			21878-54-6 (cis) 21866-72-8 (trans)	55[b]	180–182	36866-95-2
11			21854-58-0	62	217–219	21854-66-0
12			21866-65-9 (cis) 21866-74-0 (trans)	57[c]	119–125	36866-97-4
13			36872-10-3 (cis) 36872-11-4 (trans)	40[b]		
14		 (*via* **19**)	21854-64-8	54	165–166	21854-67-1
15	PhCHO		104-55-2	64	200–201	1237-69-0
16	*p*-MePhCHO		1504-75-2	57	40–42[d]	
17	*p*-MeOPhCHO		1963-36-6	61	58[d]	
18	3,4-$(MeO)_2$PhCHO		4497-40-9	53	83–84[d]	
19			505-57-7	61	144–145	1560-68-5
20			2463-53-8	50	124–125	1726-79-0
21			26370-28-5	53	113–114	3013-11-4
22	*p*-O_2NPhCHO		1734-79-8	60	117–118[d]	
23				28[e]	200–202	1686-81-3
24				14[f]	66–67[d]	

TABLE IX (*Continued*)

Entry	Carbonyl component	α,β-Unsaturated aldehydes	Registry no.	Overall yield, %	2,4-DNP, mp, °C	Registry no.
25				23[f]	36–37[d]	
26			13466-40-5	61	37–39[d]	
27	PhCHO	 (*via* 19)	13702-35-7	63	240–241	13694-45-6

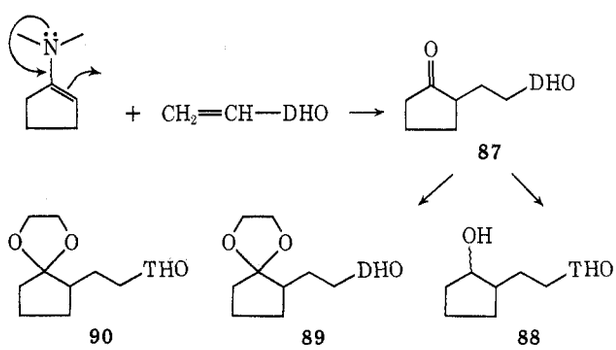
[a] Isolated as a three-component mixture (1:1:1) of isomers; cis, trans, endo. [b] Geometric isomers (40:60). [c] Geometric isomers (80:20). [d] Melting point of aldehyde. [e] Isolated in 54% yield as the 2,4-DNP derivative. [f] L. S. Davies and G. Jones, *J. Chem. Soc. C*, 2572 (1971). [g] Semicarbazone derivative.

attributed to the greater ionic (and nucleophilic) character of the C–MgX bond *vs.* the C–Li bond. Borohydride reduction of **85** followed by oxalic acid cleavage provided 2-methyl-3-phenylpropanol (**86**) in



66% overall yield from **21**. The nature of the alkyl halide used as the intercepting electrophile appears to be limited to alkyl iodides only. Other highly electrophilic halides (allyl bromide, benzyl bromide) were also found to be satisfactory, whereas alkyl bromides and chlorides were unable to compete efficiently with the anionic polymerization process. The nucleophilic agent is seemingly limited, in aprotic media, to Grignard reagents, since lithium diphenylphosphide and alkyllithium reagents failed to allow clean addition. The use of cupric and magnesium salts to stabilize the carbanion **84** met with only limited success and was not pursued further. The need for *2.0 equiv* of Grignard reagent to effect complete addition was also observed. The use of 1.0 equiv gave ~50% reaction to **85**. This suggests a previously formed complex[37] between the vinyl oxazine and the Grignard reagent followed by addition of the second equivalent to form the adduct.

In view of the failure to generate the anion of 2-alkyl oxazines and limit the alkylation to the 2-methyloxazine **18**, this vinyl addition is significant since it now allows the preparation of α-alkyl aldehydes (Table X). Of additional interest is the fact that **21** may be utilized as a "protected" acrolein which undergoes 1,4 addition of Grignard reagents followed by alkylation of the intermediate α carbanion. This sequence is difficult utilizing acrolein, which is known to produce mainly 1,2-addition products with organometallics.[28] The vinyl oxazine was also found to undergo smooth reaction with enamines producing the alkylated pentanone **87**. Reduction with sodium borohydride under previously described conditions afforded the hydroxytetrahydro-1,3-oxazine **88**. However, it was possible to convert **87** to its dioxolane derivative **89** and reduce the C=N link in the dihydro-1,3-oxazine to the aldehyde



precursor **90**. These transformations demonstrate that it is now possible to carry out normal enamine additions to acrolein without the spontaneous cyclization (although a useful one) to the bicyclic ketones.[38] This aspect is under further study.

Experimental Section[39]

2-Substituted 4,4,6-Trimethyl-5,6-dihydro-1,3-oxazines.—The following general procedure, which represents a modification of Ritter and Tillmanns,[16] was used in preparing all the oxazines **18–21** except where otherwise noted.

2-Methyloxazine (18).—To a 2-l. flask equipped with a thermometer, a stirrer, and a 250-ml addition funnel was added 400 ml of concentrated (95–97%) sulfuric acid. The acid was cooled to 0–5° with an ice bath and 90.2 g (2.2 mol) of acetonitrile was added at such a rate that the temperature was maintained at 0–5°. After the addition of the nitrile was complete, 236 g (2.0 mol) of 2-methyl-2,4-pentanediol was also added at such a rate that the same temperature (0–5°) was maintained. The mixture was stirred for an additional 1 hr and then poured onto ~1500 g of crushed ice. The aqueous solution was extracted with four 125-ml portions of chloroform (and the chloroform extracts were discarded). The aqueous solution was made alkaline with 40% sodium hydroxide solution; ice was periodically added during the addition of the sodium hydroxide solution to keep the mixture cool (below 35°). Upon becoming basic, a yellow oil appeared, which was separated. The aqueous layer was extracted with three 100-ml portions of diethyl ether, and the combined ether extracts and oil were dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation, and the residue was distilled through a 25-cm fractionating column to give 183.2 g (65%) of 2,4,4,6-tetramethyldihydro-1,3-oxazine: bp 47–49° (17 mm) (the product foamed badly during distillation; this was avoided by distillation from glass wool); ir (neat) 1667, 1442 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (s, 6), 1.22 (d, 3), 1.77 (s, 3), 4.04 (m, 1).

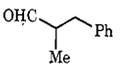
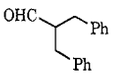
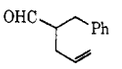
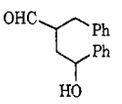
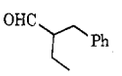
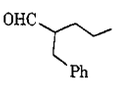
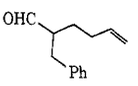
(37) E. C. Ashby, *Quart. Rev. Chem. Soc.*, **21**, 259 (1967).

(38) G. Stork and H. K. Landesman, *J. Amer. Chem. Soc.*, **78**, 5129 (1956).

(39) All melting points and boiling points are uncorrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn., and Midwest Microlabs, Inc., Indianapolis, Ind.

TABLE X

α,β-DIALKYLPROPIONALDEHYDES FROM 2-VINYL-5,6-DIHYDRO-1,3-OXAZINE (21)

Entry	RMgBr	RX	Registry no.	Aldehyde	Yield, %	2,4-DNP mp, °C	Registry no.
1	Ph	Me	5445-77-2		66	122–123[a]	
2	Ph	$PhCH_2Br$	22859-80-9		55	165–166	24569-55-9
3	Ph	$CH_2{=}CHCH_2Br$	22859-81-0		49	125–126	24569-56-0
4	Ph		36867-08-0		40[b]	169–172	36867-48-8 36867-16-0 (hemi-acetal)
5	Ph	EtI	24569-60-6		30	114–115[c]	
6	Me	$PhCH_2Br$					
7	Et	$PhCH_2Br$	22859-83-2		70	86–87	24612-95-1
8	$CH_2{=}CHCH_2$	$PhCH_2Br$	22859-84-3		30	76–77	24612-96-2

[a] Semicarbazone [R. Lucas and L. Labaune, *Ann. Chim. (Paris)*, **16**, 293 (1931)]; mp 123–124°. [b] Exists in tautomeric equilibrium with cyclic hemiacetal. [c] I. Scriabine, *Bull. Soc. Chim. Fr.*, 1194 (1961); mp 114–115°.

2-Benzyloxazine (19) was prepared in exactly the same manner as the 2-methyl derivative, using the following quantities: (a) 118 g (1.0 mol) of 2-methyl-2,4-pentanediol; (b) 128.7 g (1.1 mol) of phenylacetonitrile; (c) 200 ml of 95–98% sulfuric acid. The yield was 107–115 g (49–53%) of a straw-yellow liquid: bp 78–80° (0.25 mm); ir (neat) 1660, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.08 (s, 6), 3.32 (s, 2), 4.04 (m, 1), 7.18 (m, 5).

2-Carboethoxymethyloxazine (20) was prepared in the same manner as the 2-methyl derivative, using the following quantities: (a) 118 g (1.0 mol) of 2-methyl-2,4-pentanediol; (b) 124.3 g (1.1 mol) of ethyl cyanoacetate; (c) 200 ml of 95–98% sulfuric acid. The yield was 95 g (45%) of a clear, colorless oil which solidified on standing at −20°: bp 69–71° (0.25 mm); ir (neat) 3180, 1740, 1670, 1640 cm^{-1}; nmr (neat) δ 1.1–1.9 (m, 14), 3.05 (s, 1), 3.8–4.3 (m, 4). These signals are consistent with an approximately 1:1 mixture of endo and exo tautomers. *Note.* Care was taken to add the glycol at 0 to −10° to avoid hydrolysis of the ethyl cyanoacetate. In the neutralization step (sodium hydroxide solution) the temperature was kept between 0 and 10° and extraction of the ester oxazine with ether was performed as quickly as possible.

Alternate Procedures for Preparation of 20.—Instead of maintaining a temperature of 0–5° with an ice bath, a Dry Ice–acetone bath was used to keep the reaction mixture at −20 to −15° during the addition of the diol. After the diol addition was complete, the reaction was stirred at 0° for 2 hr. During this period careful scrutiny was necessary to assure constancy of the temperature. Since much unreacted diol is present in the mixture during much of this stirring time, allowing the reaction to warm above 3° accelerates the reaction essentially out of control. The work-up was identical with that previously described. Using this lower temperature method the yield of **20** was improved from 45 to 57%. Furthermore, since the lower temperature and greater cooling efficiency of the Dry Ice system allowed the diol to be added faster, the reaction time was actually shorter than that for the ice bath cooled reaction. If desired, the nitrile may also be added under the lower temperature conditions, rather than at 0–5°.

2-Vinyloxazine (21) was prepared in exactly the same manner as the 2-methyl derivative, using the following quantities: (a) 118 g (1.0 mol) of 2-methyl 2,4-pentanediol; (b) 58.3 g (1.1 mol) of acrylonitrile; (c) 200 ml of 95–98% sulfuric acid. The yield was 100 g (66%) of a clear, colorless liquid: bp 73–74° (25 mm); ir (neat) 1652, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (s, 6), 1.30 (d, 3), 1.58 (m, 2), 4.16 (m, 1), 5.68 (m, 3). *Note.* During and after the basification step, the work-up should be carried out in a good fume hood, since this oxazine is a mild lachrymator. The compound has a tendency to polymerize on prolonged standing. This may be avoided by storing under nitrogen at 0 to −20°.

Preparation of the Anion of 2-Methyloxazine (18).—A 500-ml three-necked flask equipped with a magnetic stirring bar, a 75-ml addition funnel topped with a rubber septum, and a nitrogen inlet tube was successively evacuated and flushed with nitrogen. Anhydrous THF (100 ml) and 14.1 g (0.10 mol) of 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine was added from a syringe through the rubber septum. The stirred solution was cooled to −78° (Dry Ice–acetone bath) and 69.0 ml (0.11 mol, 1.6 *M*) of *n*-butyllithium in hexane was injected into the addition funnel. The *n*-butyllithium was added dropwise over a period of 1 hr. Approximately 1 hr[40] after the addition was complete a yellow precipitate formed. This was indicative of complete anion formation. The lithio anion may not precipitate if more than the above quantity of solvent is employed.

General Procedure for Alkylation of Lithiooxazine.—The electrophile (0.11 mol, halide, epoxide, ketone, etc.) in 25 ml of anhydrous THF was injected into the addition funnel and slowly added to the mixture over a period of ~30 min. The reaction mixture was allowed to slowly warm to room temperature, at which time the yellow precipitate disappeared. The mixture was then poured into ~100 ml of ice–water and acidified (pH 2–3) with 9 *N* hydrochloric acid. The acidic solution was extracted with three 75-ml portions of pentane (discarded) and made basic by the careful addition of 40% sodium hydroxide solution. Ice was added to keep the mixture cool during the neutralization. The resulting oil was extracted with three 75-ml portions of ether and the ether extracts were dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation to give the crude alkylated dihydro-1,3-oxazine (90–98%).

General Procedure for Reduction of the Dihydro-1,3-oxazine.—To a 600-ml beaker was added 100 ml of THF, 100 ml of 95% ethyl alcohol, and the crude dihydrooxazine obtained in the preceding experiment. The mixture was cooled between −35 and −40° with an acetone bath to which Dry Ice was added. Hydrochloric acid (9 *N*) was added to the magnetically stirred solution until an approximate pH of 7 was obtained. Sodium borohydride solution was prepared by dissolving 3.78 g (0.10

(40) The use of *tert*-butyllithium in place of *n*-butyllithium will generate the anion in a few minutes, thus shortening the procedure.

mol) in a minimum amount of water (~4–5 ml) in which 1 drop of 40% sodium hydroxide was present. The sodium borohydride solution and the 9 *N* hydrochloric acid solution were introduced to the stirred solution alternately so that pH 6–8 was maintained.[41] The pH was monitored by periodic checks with pH paper. During the addition care was taken to maintain a temperature between −35 and −45°. After addition of this borohydride solution was complete, the solution was stirred with cooling for an additional 1 hr (pH 7 was maintained by the occasional addition of hydrochloric acid solution).

The contents were then poured into ~100 ml of water and made basic by the addition of 40% sodium hydroxide solution. The layers were separated and the aqueous solution was extracted with three 75-ml portions of diethyl ether. The combined organic extracts were washed with 100 ml of saturated sodium chloride solution and dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation to give the crude tetrahydrooxazine (90–99%).

Cleavage of the Tetrahydrooxazine to the Aldehyde. A. Steam Distillation.—To a 250-ml flask equipped with a distillation head and an addition funnel with a nitrogen tube was added 50.4 g (0.40 mol) of hydrated oxalic acid and ~150 ml of water. Steam was introduced into the solution and the tetrahydrooxazine (~0.1 mol) was added dropwise over a period of 20 min. The addition funnel was then washed down with 5 ml of 1 *M* oxalic acid. The steam distillation was continued until the distillate was free of organic material. The distillate was extracted with three 50-ml portions of pentane or ether. The extracts were dried over anhydrous sodium sulfate and the solvent was removed to give the pure aldehyde. In some instances distillation of the product was necessary.

B. Oxalic Acid Hydrolysis.[42]—In cases where the aldehyde was water soluble or insufficiently volatile to make steam distillation practical, the following procedure was used. The crude tetrahydro-1,3-oxazine (0.1 mol) was added to the oxalic acid solution prepared above and heated to reflux for 2 hr. The cloudy solution was extracted with ether, pentane, or dichloromethane (depending on the nature of the aldehyde) and the extracts were washed with 5% sodium bicarbonate solution and dried (Na_2SO_4). Concentration of the solution was followed by either distillation or recrystallization.

Direct Conversion of Tetrahydro-1,3-oxazine (40) to Oxime 42.[43]—A solution of 4.00 g (18 mmol) of **40** in 40 ml of absolute ethanol was treated with 6.2 g (90 mmol) of hydroxylamine hydrochloride and heated under reflux for 8–15 hr. The solution was poured into 100 ml of cold 1.2 *N* hydrochloric acid and extracted with ether. After drying (K_2CO_3) and concentration, there was obtained 2.18 g of the crude oxime. Distillation gave a colorless oil, bp 64–65° (0.3 mm), which solidified: mp 29–32°; nmr ($CDCl_3$) δ 9.60, 7.47, 6.80, 5.67, 1.0–2.5.

Anal. Calcd for $C_8H_{13}NO$: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.30; H, 9.46; N, 9.87.

General Procedure for the Preparation of Cycloalkane Carboxaldehydes (Table VI, Entries 14–16, 22–24).—To a 500-ml three-necked, round-bottom flask equipped with a nitrogen inlet tube, a rubber septum, and a magnetic stirrer was added 250 ml of THF and 10.9 g (0.05 mol) of 2-benzyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (**19**). The mixture was cooled to −78° and 32.0 ml (0.06 mol, 1.6 *M*) of *n*-butyllithium in hexane was slowly added. After 1 hr of stirring, 11.5 g (0.05 mol) of 1,4-dibromobutane was added and allowed to react for 0.5 hr. *n*-Butyllithium (0.06 mol) was again added and the mixture was allowed to warm slowly to −50° and maintained at that temperature for 2 hr. The mixture was then poured into 150 ml of water and crushed ice, acidified to pH 2–3, and extracted with ether. The ether extract was discarded. The aqueous solution was basified with 40% sodium hydroxide and extracted with ether. The ether extract was dried over potassium carbonate and the solvent was removed by rotary evaporation, leaving the 2-cycloalkyloxazine (90–97%).

When the 2-methyl oxazine **18** was employed, the *cyclization* step was carried out using 2 equiv of butyllithium, since yields were found to be generally lower when only 1 equiv was employed.

The reduction and cleavage of the oxazine to the cycloalkane carboxaldehydes was performed using the procedures given above.

General Procedure for Preparation of Ethyl α-Formyl-α-alkylacetates (Table VI, Entries 25–28).—The following procedure for the preparation of the α-ethyl formyl ester (entry 25) is typical of compounds in this series.

A solution prepared by adding 63.9 g (0.30 mol) of **20** to 200 ml of tetrahydrofuran and purging with nitrogen was treated with 37.0 g (0.33 mol) of potassium *tert*-butoxide at room temperature. The resulting white suspension was stirred at room temperature for 1 hr and then cooled to 0°. A mixture of 32.7 g (0.30 mol) of ethyl bromide and 15 ml of tetrahydrofuran was added dropwise over a 45-min period and stirring was continued for 14 hr thereafter. The mixture was quenched in 300 ml of water and acidified (pH ~3) with dilute hydrochloric acid. After several pentane extractions, the aqueous solution was rendered alkaline (pH 7–9) with 20% sodium hydroxide and extracted with ether, dried ($MgSO_4$), and concentrated, giving 61.9 g (86%) of a yellow oil. Gas chromatography indicated 2% starting oxazine ester **20**, 2% diethylated material (**37**, R = Et), and 96% monoethylated product (**36**, R = Et). The latter (52.3 g, 0.22 mol) was reduced by dissolving in 500 ml of 1:1 ethanol–tetrahydrofuran, cooling to −35 to −40°, and keeping the *pH at 5–6* by periodic adjustment with 9 *N* hydrochloric acid. The sodium borohydride (9.45 g, 0.25 mol) was introduced as previously described, and the pH during the addition[44] was kept between 5 and 6. After addition of borohydride, the mixture was stirred for an additional 1 hr and then poured into 250 ml of water and made alkaline (pH 7–8) by the addition of sodium hydroxide solution. Extraction with ether followed by drying (K_2CO_3) and concentration left 47.8 g (91%) of the tetrahydro-1,3-oxazine. The latter was hydrolyzed directly by gentle reflux in a solution of 87.7 g (0.70 mol) of oxalic acid in 250 ml of water for 2 hr. Extraction of the aqueous mixture with dichloromethane followed by washing the organic extract with aqueous sodium bicarbonate (5%), drying with sodium sulfate, and concentration left 19.0 g of a yellow oil. Distillation gave 14.0 g (57%) of a colorless liquid: bp 60–62° (11 mm);[45] ir (neat) 3330, 2710, 1740, 1720 cm^{-1}; nmr (CCl_4) δ 11.4, 9.7, 7.0, 4.3, 3.1, 2.3–1.6, 1.5–0.8. These data are consistent with a tautomeric mixture (1:1) of the enol–aldo forms.

General Procedure for Preparing 1-Formyl-1-carboethoxy Cycloalkanes (Table VI, Entry 30, 31).—The preparation of entry 30 (Table VI) is typical. To a solution of 4.25 g (20 mmol) of **20** in 25 ml of anhydrous tetrahydrofuran was added, under nitrogen, a suspension of 0.53 g (22 mmol) of sodium hydride in 25 ml of tetrahydrofuran. After hydrogen evolution had ceased, the mixture was warmed for 15 min at 60° and then cooled to −78°. The resulting suspension was treated with 4.75 g (22 mmol) of 1,4-dibromobutane and allowed to warm to room temperature (1.5 hr). The solution was again cooled to −78° and 0.53 g (22 mmol) of sodium hydride, as a suspension in 10 ml of tetrahydrofuran, was added. The mixture was stirred at room temperature overnight and then quenched with 100 ml of ice–water and acidified to pH 2–3 with 9 *N* hydrochloric acid. The acidic solution was extracted with pentane and the pentane extracts were discarded. The aqueous solution was made basic by slow addition of 40% sodium hydroxide and the resulting oil was removed by extraction with ether. The extracts were washed with water, dried (Na_2SO_4), and concentrated, leaving crude cycloalkyloxazine [**37**, R = $(CH_2)_4$]. Reduction of **37** was performed on 4.62 g (17.2 mmol) and using 0.6 g of sodium borohydride according to the general reduction procedure described above. After the isolation there was obtained 4.4 g of a light yellow oil (95%), ir 3200–3500, 1730 cm^{-1}. The C=N absorption at 1670 cm^{-1} was absent. The product (4.1 g) was cleaved without any purification by the steam distillation procedure from an aqueous oxalic acid solution (7.6 g in 100 ml) affording 2.7 g of 1-formyl-1-carboethoxycyclopentane (67%), ir (neat) 1700–1750 cm^{-1} (broad), 2,4-DNP mp 134–134.5°.

(41) It is convenient to introduce the acid and hydride solutions from two 50-ml burets placed above the beaker.

(42) It has been found that this procedure for isolating *all* the aldehydes prepared by this method is quite satisfactory, since steam distillation, in many instances, required prolonged heating that consumed considerable time. However, certain acid-sensitive aldehydes (*i.e.*, cyclopropane, phenylcyclopropane carboxaldehydes) are best isolated by steam distillation, since their contact time in the acid medium is minimized.

(43) We thank Dr. John F. Hansen for this experiment.

(44) Owing to the weaker base strength of this oxazine, reduction was more successful at lower pH values.

(45) Bp 71–75° (22 mm): H. Watanabe, A. Ide, N. Sugimoto, Y. Noguchi, R. Ishida, and Y. Kowa, *Yakugaku Zasshi*, **83**, 1118 (1963).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.44; H, 8.27.

Reaction of Lithiooxazine with *n*-Butyl Tosylate to 22.—Using the procedure described for formation of the lithio salt of **18** (2.82 g of **18**, 13.5 ml of *n*-butyllithium) was added 4.9 g of *n*-butyl tosylate at −78°. The solution immediately turned to a crimson color. After stirring at room temperature for 15 hr, the solution was quenched in water and worked up *via* the acid–base treatment. The crude recovered ether concentrate contained a solid which was separated by addition of pentane. Filtration gave 1.71 g (10%) of a crystalline product: mp 135–136°; ir (Nujol) 1650, 1158, 1082 cm^{-1}; nmr ($CDCl_3$) δ 7.88 (d, J = 8 Hz), 7.40 (d, J = 8 Hz, 2), 4.05 (m, 1), 4.00 (m, 2), 2.5–2.6 (m, 5), 1.1–1.2 (m, 6).

The pentane solution was evaporated and the residue was distilled to give 2.53 g (89%) of **18**.

Dimerization of Lithio Salt of 18 to 30.—A solution of **18** (6.21 g, 44 mmol) in 50 ml of tetrahydrofuran was treated with 21.5 ml (2.23 M) of *n*-butyllithium in hexane at −78° under nitrogen. The solution was allowed to warm to room temperature and then poured into water, extracted with ether, dried (K_2CO_3), and concentrated. The viscous oil was distilled at 88–92° (0.01 mm), keeping the pot temperature below 130°, which afforded 5.2 g (84%) of the dimer **30**, ir (neat) 3220, 1660 cm^{-1}.

Anal. Calcd for $C_{16}H_{30}N_2O_2$: C, 68.04; H, 10.71; N, 9.92. Found: C, 67.89; H, 10.83; N, 9.98.

Heating **30** at 190–195° under nitrogen gave pure **18** which was identical with an authentic sample.

Dimerization of Lithio Salt of 18a to 30a.—The anion of **18a** was prepared as above using 4.01 g (26 mmol) in 30 ml of tetrahydrofuran and 12.1 ml of butyllithium. Evaporation of the ethereal extract gave 3.52 g (88%) of dimer **30a**, bp 92° (0.01 mm), ir (neat) 3210, 1660 cm^{-1}.

Anal. Calcd for $C_{18}H_{34}N_2O_2$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.90; H, 10.96; N, 8.83.

Heating at 190–200° led to pure **18a** shown to be identical with an authentic sample.

Conversion of 18b to the Ketenimine Trimethylsilyl Ether 28.—A solution containing 22.2 g (22 mmol) of diisopropylamine in 150 ml of anhydrous tetrahydrofuran was cooled under nitrogen to −50° and 22 mmol of *n*-butyllithium in hexane was added. The temperature of the solution containing lithium diisopropylamide was allowed to warm to 0° and 33.7 g (20 mmol) of **18b** was added dropwise. The yellow solution was then warmed to room temperature and stirred for 2.5 hr, at which time it was cooled again to 0°. The addition of 22.0 g (20 mmol) of trimethylchlorosilane followed in a dropwise fashion as the solution turned cloudy. After 2 hr of additional stirring at 25°, the salts were removed by filtration and the solvents were removed by rotary evaporation. The residue was distilled to give 36.1 g (75%) of pure ketenimine **28**, bp 65–68° (0.3 mm), ir (neat) 2050, 843 cm^{-1}.

Anal. Calcd for $C_{13}H_{27}NOSi$: C, 64.67; H, 11.27; N, 5.80. Found: C, 64.98; H, 11.17; N, 6.03.

Reaction of Benzyloxazine 19 with Ethyl Iodide. A. Using *n*-Butyllithium.—A solution of 10.85 g of **19** in 40 ml of tetrahydrofuran was treated with 20 ml of *n*-butyllithium at −78°. After 1 hr, ethyl iodide (8.6 g) was added and the solution was warmed to room temperature. The product **31** was isolated in the usual fashion: 11.8 g (96%); bp 93–96° (0.20 mm); ir (neat) 1665 cm^{-1}; nmr (CCl_4) δ 4.03 (m, 1), 3.2 (d of d, 1).

Anal. Calcd for $C_{16}H_{23}NO$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.09; H, 9.48; N, 5.63.

B. Using Dimethylsulfinyl Carbanion.—A solution of 6.8 g of **19** in 5 ml of DMSO was added to a solution of dimethylsulfinyl carbanion (from 2.0 g of sodium hydride in 20 ml of DMSO)[21] at room temperature and the mixture was stirred for 3 hr. The addition of 7.8 g of ethyl iodide followed dropwise with external cooling to keep the reaction temperature at 25–27°. After 30 min the mixture was poured into water, and the organic layer was removed by ethereal extraction and concentrated to give **31** (84%) which was identical with the product from *n*-butyllithium treatment.

Reaction of 2-(α-Ethyl)benzyloxazine (31) with Methyl Iodide at −78°.—Reaction of 2.47 g of **31** with 1.1 equiv (5.0 ml) of *n*-butyllithium in 30 ml of tetrahydrofuran gave the orange-colored anion after 45 min. To this mixture was added 1.1 equiv of methyl iodide and the solution was stirred for 3 hr at −78°, after which 20 ml of water was slowly added. The aqueous solution upon reaching ambient temperature was diluted with 50 ml of water and extracted several times with ether, dried (K_2CO_3), and concentrated to give 2.5 g (96%) of **32**: bp 90–94° (0.24 mm); ir (neat) 1665 cm^{-1}; nmr (CCl_4) δ 4.03 (m, 1). The signals at δ 3.2 were absent.

Anal. Calcd for $C_{17}H_{25}NO$: C, 78.72; H, 9.71; N, 5.40. Found: C, 78.60; H, 9.68; N, 5.30.

Reaction of 31 with Ethylmagnesium Bromide at 25°.—To a solution of 2.5 g of **31** in 30 ml of tetrahydrofuran was added 1.0 equiv of *n*-butyllithium at −78°. The solution was allowed to warm to ambient temperature, where the color had changed from orange to dark amber. A solution of ethylmagnesium bromide (3.0 equiv) in ether was slowly added and a mild exothermic reaction ensued. Stirring was continued at room temperature for 12 hr and the mixture was poured into 50 ml of water. Extraction with ether, drying of the extracts, and concentration left 2.91 g of an oil whose infrared spectrum showed only a small C=N absorption at 1665 cm^{-1}. This product was heated for 1.5 hr in an oxalic acid solution (5 g per 40 ml) and then the aqueous solution was extracted with ether. Concentration of the dried ethereal extracts afforded 1.64 g (92%) of 4-phenyl-3-hexanone (**33**), semicarbazone mp 138–140° (lit.[46] 139–140°).

Alkylation of Ester Oxazine 20 with Alkyl Halides in Acetonitrile. Formation of 36 (R = Allyl).—A mixture containing 21.3 g (10 mmol) of **20**, 16.8 g (10 mmol) of allyl iodide, and 10 ml of dry acetonitrile was heated under reflux for 24 hr. The solvent was removed *in vacuo* and the residue was washed with cold 5% sodium hydroxide solution and taken up in ether. The latter extracts were washed once with saturated brine solution, dried (K_2CO_3), and concentrated to give 22.4 g of an oil which was distilled bulb to bulb. The yield was 21.1 g (84%) of a colorless liquid. Tlc examination indicated spots for monoalkylated **36**, starting material **20**, and dialkylated oxazine **37** (ether–pentane, 70:30). Vpc analysis showed the mixture to be 71:7:22, respectively. This mixture was used to prepare the 2-alkyl formyl ester (Table VI, entry 28) without further purification.

Ethyl 2-Formyl-2-allylacetate (Table VI, Entry 28).—The general procedure for borohydride reduction was used except that the pH during the reaction was kept between 4 and 6. The quantities utilized were 12.15 g of the above oxazine mixture, 1.89 g of sodium borohydride, 50 ml of ethanol, and 50 ml of tetrahydrofuran. This process gave 11.1 g of reduced oxazine which exhibited only a weak band for the C=N link at 1660 cm^{-1} owing to the inert dialkylated oxazine **37**. The aldehyde was released by addition of the reduced oxazine (11.1 g) to a refluxing solution of 15 g of oxalic acid dihydrate in 150 ml of water and collecting the steam distillate. Extraction of the organic layer with ether and concentration gave 3.8 g (44% overall from **20**) of the aldehyde: ir (neat) 3500–3400, 3080, 1670, 1720 cm^{-1}; nmr (CCl_4) δ 9.68 (d, 0.4 H), 7.0 (br s, 0.6 H) 4.8–6.2 (m, 3), 4.2 (q of d, 2), 3.3 (m, 0.4 H), 2.7 (m, 2), 1.3 (m, 3). The spectrum corresponded to a 40:60 tautomeric mixture of enol–aldo forms.

***cis*-4-Heptenal (50).**—The 2-(3-hexynyl) oxazine **49** was prepared by the general procedure for alkylation of **18** using 42 g (0.41 mol) of 1-chloro-2-pentyne,[47] 52.5 g (0.37 mol) of **18**, and 262 ml of *n*-butyllithium. The yield of **49** was 72.5 g (95%), bp 60–62° (1.2 mm), ir (neat) 1665 cm^{-1}.

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21; N, 6.76. Found: C, 75.03; H, 10.28; N, 6.94.

The reduction of the triple bond in **49** was performed using 20.7 g (0.10 mol) and 1.7 g of 5% Pd on barium sulfate in 25 ml of pyridine. The solution was hydrogenated in a Paar apparatus at 39 psi for 25–45 min. The catalyst was removed by filtration through Celite and washed with pentane. Removal of the mixed solvents by rotary evaporation left 20.0 g (95%) of the olefin oxazine: bp 60–61° (1.0 mm); ir (neat) 1665 cm^{-1}; nmr ($CDCl_3$) δ 5.2–5.6 (t, 2).

Anal. Calcd for $C_{13}H_{23}NO$: C, 74.59; H, 11.07; N, 6.69. Found: C, 74.29; H, 11.28; N, 6.92.

Reduction of the dihydro-1,3-oxazine was accomplished according to the general procedure using 67.4 g (0.32 mol) of the olefinic oxazine, 12.3 g (0.32 mol) of sodium borohydride, and

(46) "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p 2694.

(47) Prepared according to the procedure described by A. I. Meyers and E. W. Collington, *J. Org. Chem.*, **36**, 3044 (1971), in 90% yield. The crude materials gave satisfactory alkylation results.

500 ml of 1:1 ethanol–THF. The yield of the tetrahydro-1,3-oxazine was 67.2 g (98%): bp 62–64° (0.08 mm); ir (neat) 3500–3300, 1650 cm^{-1}; nmr ($CDCl_3$) δ 5.3 (m, 2), 4.2 (t, 1), 3.7 (m, 1).

Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.79; H, 12.15; N, 6.38.

The aldehyde **50** was released by the steam distillation method using 33 g of the above tetrahydro-1,3-oxazine, 78 g of oxalic acid, and 240 ml of water. The steam distillate was saturated with salt and extracted with ether (3 × 100 ml), dried (K_2CO_3), and concentrated. Distillation of the residue showed little change in purity, bp 28–30° (2 mm). The yield of **50** was 9.45 g (54%): ir (neat) 2710, 1725, 1650, 970 cm^{-1}; nmr (CCl_4) δ 10.33 (t, 1), 5.4 (m, 2); 2,4-DNP mp 93–94° (ethanol).[48]

2-(6-Bromohexyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (52).—The lithio salt of **18** (40 mmol) was prepared according to the general procedure at −78°. A rapid injection of 6.9 g (60 mmol) of 1,5-dibromopentane was followed by stirring at room temperature for 4–15 hr and the mixture was poured into ice–water and acidified (pH 2–3) with 9 *N* hydrochloric acid. Extraction with pentane removed excess dibromopentane and the aqueous solution was then rendered alkaline to free the oxazine. The latter was removed by several ethereal extractions, dried (K_2CO_3), and concentrated *in vacuo* at room temperature, leaving 10.5 g (90%) as a pale yellow oil. Although this material was suitable for most subsequent reactions, it was distilled, bp 90° (0.05 mm), as a colorless liquid (75%): ir (neat) 1665 cm^{-1}; nmr (CCl_4) δ 4.0 (m, 1, –CHO–), 3.35 (t, 2, CH_2Br).

Anal. Calcd for $C_{13}H_{24}NOBr$: C, 53.84; H, 8.34; N, 4.83. Found: C, 53.61; H. 8.46; N, 4.93.

2-(5-Bromopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (52, One Less Methylene Group).—The procedure was identical with that of **52** except that 1,4-dibromobutane was used. Concentration of the ethereal extracts was done at or below room temperature in order to avoid intramolecular salt formation. Distillation through a short-path column gave pure bromopentyl oxazine (61%): bp 67° (0.075 mm), with the pot temperature not allowed to exceed 110°; ir (neat) 1664 cm^{-1}; nmr (CCl_4) δ 3.35 (t, 2, CH_2Br).

Anal. Calcd for $C_{12}H_{22}NOBr$: C, 52.17; H, 8.03; N, 5.08. Found: C, 52.45; H, 8.19; N, 5.09.

Bicyclic Oxazinium Salt 63.—If the above distillation is carried out with a pot temperature in excess of 120° or if the crude ether concentrate is warmed overnight at 120–125°, a solidified mass forms. Recrystallization from acetonitrile–ether gave colorless crystalline material: mp 184–185° (50%); ir (KBr) 1625 cm^{-1} ($OC{=}N{<}$)$^+$; nmr ($CDCl_3$) δ 5.03 (m, 1, –CHO–).

Anal. Calcd for $C_{12}H_{22}NOBr$: C, 52.17; H, 8.03; N, 5.08. Found: C, 52.10; H, 8.10; N, 5.10.

Bicyclic oxazinium salt 62 was prepared from the lithio salt of **18** and 1,3-dibromopropane (1.0 equiv) under the general procedure for alkylation. Upon isolation of the 2-(2-bromobutyl)oxazine a solid appeared which was collected by filtration. The bromide salt of **62** was hygroscopic and was converted to the perchlorate salt by treating an equimolar mixture of the bromide and silver perchlorate in acetonitrile, mp 201–202°, ir (Nujol) 1635 cm^{-1}.

Anal. Calcd for $C_{11}H_{20}NO_5Cl$: C, 47.00; H, 7.12; N, 4.98. Found: C, 46.94; H, 7.00; N, 5.03.

2-(5-Chloropentyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine.—The lithio anion of the 2-methyl oxazine (40 mmol in 40 ml of THF) was prepared as usual and 44 mmol of 1-bromo-4-chlorobutane was added *via* a syringe all at once. The standard isolation procedure yielded the chloropentyl oxazine in 95% crude yield. Distillation gave 87% pure material: bp 59° (0.12 mm); ir (neat) 1665 cm^{-1}; nmr (CCl_4) δ 3.5 (t, 2, CH_2Cl). There was no decomposition or quaternization during the distillaton.

Anal. Calcd for $C_{12}H_{22}NOCl$: C, 62.17; H, 9.52; N, 6.04. Found: C, 62.38; H, 9.58; N, 5.88.

2-(6-Cyanohexyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (54).—A solution of 14.5 g (50 mmol) of 6-bromohexyl oxazine **52** and 2.65 g of sodium cyanide in 25 ml of dimethyl sulfoxide was stirred at room temperature for 1 hr and then heated at 55° for 2 hr. Stirring was continued for an additional 15 hr (25°) and the mixture was poured into 50 ml of 5% sodium carbonate. The aqueous solution was extracted with ether and the ethereal extracts were washed with cold 1 *N* hydrochloric acid to remove the cyano oxazine. The acidic solution was neutralized with aqueous alkali and then extracted with ether. Drying and concentration left an oil (95%) which was distilled, bp 95° (0.1 mm), to afford pure product (90%): ir (neat) 2245, 1660 cm^{-1}; nmr (CCl_4) δ 4.05 (m, 1, –CHO–), 2.32 (t, 2), 2.0 (t, 2); *m/e* 236. A perchlorate salt was prepared in ether, mp 75° (ethanol–ether).

Anal. Calcd for $C_{14}H_{25}N_2ClO_5$: C, 49.93; H, 7.48; N, 8.31. Found: C, 49.80; H, 7.46; N, 8.08.

7-Cyanoheptaldehyde (55) was prepared by the general procedure of borohydride reduction followed by oxalic acid hydrolysis and extraction with ether. The overall yield from **18** was 47%: ir (neat) 2718, 2240, 1718 cm^{-1}; nmr (CCl_4) δ 9.7 (t, 1); 2,4-DNP mp 76–77° (lit.[49]).

2-(6-Carboethoxyhexyl)-4,4,6-trimethyloxazine (56).—The cyanohexyl oxazine (**54**, 4.72 g) was dissolved in 95% ethanol and cooled in an ice bath as hydrogen chloride was slowly passed through for 1 hr. The solution was brought to gentle reflux for 12 hr as the ammonium chloride suspension appeared. Upon cooling and filtering off the salt, the ethanol solution was concentrated and the residue was dissolved in water and neutralized with 5% sodium carbonate. Ether extraction followed by drying (K_2CO_3) and concentration left 4.7 g (82%) of the ester **56**. Purification was accomplished either by (a) elution from Woelm alumina I with ether or (b) distillation: bp 100° (0.025 mm); ir (neat) 1737, 1666 cm^{-1}; nmr (CCl_4) δ 4.08 (m, 3, –CHO–).

Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.98; H, 10.33; N, 5.05.

Ethyl 7-Formylheptanoate (57) was prepared from **56** by the general procedures for reduction and oxalic acid hydrolysis followed by ether extraction: ir (neat) 2711, 1730 cm^{-1}; nmr (CCl_4) δ 9.74 (t, 1); 2,4-DNP mp 57–58°.

2-(6-Benzoylhexyl)-4,4,6-trimethyldihydro-1,3-oxazine (58).—To a stirred solution of 4.72 g (20 mmol) of the 6-cyanohexyl oxazine **54** in 35 ml of ether was added 3.0 equiv of phenylmagnesium bromide (2 *M*) in ether. The two-layered solution was stirred at room temperature for 15 hr and then poured onto 15 ml of 9 *N* hydrochloric acid containing an equal volume of cracked ice. After the aqueous mixture was stirred for 20 min, it was extracted with ether several times and the ether extracts were discarded. The acid solution was neutralized by sodium bicarbonate and then extracted with ether several times. The ethereal extracts were dried (K_2CO_3) and concentrated, leaving a waxy solid **58** (5.81 g, 92%). The product was crystallized from pentane to give 5.6 g (90%) of pure **58**: mp 34–35°; ir 1688, 1665 cm^{-1}; nmr (CCl_4) δ 2.88 (t, 2, $-CH_2COPh$).

Anal. Calcd for $C_{20}H_{29}NO_2$: C, 76.15; H, 9.27; N, 4.44. Found: C, 75.92; H, 9.54; N, 4.58.

2-(7-Hydroxy-7-phenyl-*n*-heptyl)dihydro-1,3-oxazine (61).

A. From Lithium Aluminum Hydride Reduction of 58.—A solution of 3.15 g (10 mmol) of **58** in 10 ml of anhydrous ether was added dropwise to a stirred suspension of lithium aluminum hydride (0.76 g, 20 mmol) in 40 ml of ether. The mixture was stirred for 30 min and quenched with wet ether followed by 2 ml of 10% sodium hydroxide solution. The precipitated salts were removed by filtration and washed with ether. The combined ethereal solution was washed with saturated brine solution, dried (Na_2SO_4), and concentrated, leaving a colorless solid (recrystallized from pentane), 2.93 g (92%) of the hydroxy oxazine **61**: mp 45°; ir 3200, 1658, 1605 cm^{-1}; nmr (CCl_4) δ 7.23 (br s, 5, C_6H_5), 4.58 (t, 1, CHOH).

Anal. Calcd for $C_{20}H_{31}NO_2$: C, 75.67; H, 9.58; N, 4.41. Found: C, 75.55; H, 9.71; N, 4.55.

B. From Sodium Borohydride Reduction of 58.—The benzoyl oxazine **58** (1.57 g) was dissolved in 10 ml of 95% ethanol to which 0.5 ml of 40% sodium hydroxide had been added. To this solution was added sodium borohydride (0.19 g) dissolved in a minimum amount of water and the mixture was stirred for 1 hr at 25°. The alcohol was removed by rotary evaporation and the residue was diluted with saturated salt solution. Ether extraction followed by washing the ethereal extracts with brine, drying (Na_2SO_4), and concentration afforded **61** (1.48 g, 95%) which was identical with that obtained from the lithium aluminum hydride reduction.

Oxidation of 61 to 58 with Chromic Anhydride.—Hydroxy oxazine **61** (0.95 g, 3 mmol) in 5 ml of pyridine was added by drops to 15 mmol of chromic anhydride in 15 ml of pyridine which

(48) G. Hoffman and P. Meijoom, British Patent 1,068,712 (1963).

(49) M. Ohno, N. Naruse, S. Torimitsu, and I. Teresawa, *J. Amer. Chem. Soc.*, **88**, 3168 (1966).

had been prepared by the careful addition of the powder to pyridine. On stirring at room temperature the mixture turned very dark and was allowed to stir overnight, poured into water, and filtered. Both the solid and liquid were extracted with ether (~60 ml). The ether extract was washed with brine and concentrated to an oil. The oil was dissolved in pentane and the oxazine **58** (0.63 g, 68%) crystallized on cooling, mp 34–35°. The material was identical with a sample prepared by the addition of phenylmagnesium bromide to **54**.

7-Benzoylheptanal (**59**) was prepared in 60% yield (from **52**) by subjecting **58** to the general procedure for reduction except that the reduction mixture was acidified with 3 *N* hydrochloric acid at −40° prior to quenching. In this fashion, the carbonyl was not reduced. Oxalic acid cleavage according to the general procedure followed by ether extraction gave **59**: mp 36° (pentane); ir (neat) 2715, 1724, 1684 cm^{-1}; nmr (CCl_4) δ 9.74 (t, 1); 2,4-DNP mp 105–106°.

Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.29; H, 8.59.

A sample of **59** was oxidized *via* the Jones reagent to 7-benzoylheptanoic acid, mp 84–85° (lit.[50] mp 83–85°).

8-Hydroxy-8-phenyloctanal (**60**) was prepared in 58% yield (from **52**) by the general procedure for reduction and hydrolysis of **61**. Alternatively, **60** was prepared by reduction of **58** using twice the usual amount of sodium borohydride and allowing the reduction solution to stir at room temperature at pH 9–10 after reduction of the C=N link at −40° had been completed. The crude product was unstable toward distillation but could be readily purified *via* the bisulfate addition compound. Thus, an aqueous solution of sodium bisulfite and the crude aldehyde was extracted several times with ether and the latter extracts were discarded. Acidification to release the aldehyde followed by ether extraction and concentration of the extract gave pure **60** as an oil: ir (neat) 3400, 2720, 1720 cm^{-1}; nmr (CCl_4) δ 9.65 (t, 1), 7.2 (s, 5), 4.65 (t, 1), 3.11 (s, 1 exchanges with D_2O).

Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.07; H, 9.28.

Formation and Deuteration of Grignard Reagent 64 in THF.—To a suspension of 0.6 g of magnesium shavings in 50 ml of tetrahydrofuran was added 1–2 ml of a solution of **52** (2.90 g in 10 ml of THF). The reaction was initiated by addition of an iodine crystal or a drop of methyl iodide before the remainder of the bromohexyloxazine solution was introduced. After 2–3 hr, the complete absence of the magnesium shavings was noted and the clear solution was treated with deuterium oxide (5 ml) and stirred for an additional 30 min. The mixture was poured into ice–water, extracted with ether, dried (K_2CO_3), and concentrated to give 2-(*n*-hexyl-6-*d*)oxazine (**65**, E = D), 1.94 g (92%): bp 65–67° (0.05 mm); ir (neat) 1659 cm^{-1}; *m/e* 212 (calcd 212).

7-Deuterioheptaldehyde (**66**, **E = D**) was obtained from **64** by the general procedure for reduction and hydrolysis, bp 155°; vpc was identical with that of an authentic sample of *n*-heptanal; ir (neat) 1724, 2178 (CD), 2715 cm^{-1}; *m/e* 115. When compared to the mass spectrum of heptanal, indications were that deuteration was complete (95%).

Formation of Magnesium Bromide. Grignard Reagent 64.—To an ethereal solution containing 10 mmol of magnesium bromide (from 1.88 g of 1,2-dibromoethane and 0.60 g of magnesium shavings in 50 ml of ether) was added 2.90 g (10 mmol) of 2-(6-bromohexyl)oxazine (**52**) under a nitrogen atmosphere. The mixture was stirred for 4 hr at 25°, after which a two-layered solution resulted. The latter was used in this form for all the following experiments.

A. Ethyl Chloroformate.—The ethereal Grignard solution was cooled to 0° and 1.3 g (12 mmol) of ethyl chloroformate was rapidly added. After stirring at room temperature for 12 hr the reaction mixture was worked up by aqueous quenching, ethereal extraction, and concentration to give 2.31 g of a mixture of 2-(*n*-hexyl)oxazine (**65**, E = H) and 2-(6-carboethoxyhexyl)-oxazine (**65**, E = CO_2Et). Vpc (SE-30, 175°) examination confirmed the identity with authentic samples [36% **56**, 60% **65** (E = H)].

B. Benzaldehyde.—The ethereal solution of **64** was treated with 1.06 g (10 mmol) of benzaldehyde in 10 ml of ether by dropwise addition. The usual isolation procedure gave 2.44 g of a mixture of **65** (E = H) and **61** or **65** [E = CH(OH)Ph] in 35 and 65% yield, respectively (estimated by nmr). Pure **61** was isolated by preparative layer chromatography (1.5 mm, PF_{254}) after elution with ether (35% yield), mp 45°. This product was identical in all respects with that obtained by reduction of **58** with metal hydrides.

C. Benzonitrile.—To the refluxing Grignard solution **64** was added 1.13 g (11 mmol) of benzonitrile and heating of the mixture was continued for 24 hr. Isolation gave 2.35 g of a mixture containing **65** (E = H, 60%) and **58** (34%) as estimated by vpc (SE-30, 175°).

Reaction of 2-Benzyloxazine with 4-Bromobutyronitrile.—Generation of the benzyloxazine (**19**) carbanion in the usual manner was followed by addition of 6.5 g (44 mmol) of 4-bromobutyronitrile. After the standard isolation procedure there was obtained 7.4 g (65%) of 2-(4-cyano-1-phenylbutyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine, mp 44.5–45° (pentane), ir (film) 2255, 1662 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}N_2O$: C, 76.02; H, 8.51; N, 9.85. Found: C, 75.74; H, 8.67; N, 9.94.

2-Phenyl-6-cyanohexaldehyde (**67**).—The benzyloxazine (**19**) carbanion was generated as usual (THF, −78°) and treated with 7.12 g (44 mmol) of 5-bromovaleronitrile. After work-up, the cyano oxazine was obtained (11 g, 92%) which was shown by nmr and tlc (ether) to be >95% pure. It was used without further purification for the borohydride reduction (general procedure) and the resulting tetrahydro oxazine was hydrolyzed in oxalic acid: yield 5.20 g (65%) of oil; ir (neat) 2710, 2243, 1720 cm^{-1}; nmr (CCl_4) δ 9.66 (d, 1); 2,4-DNP mp 116.5–117°.

Anal. Calcd for $C_{19}H_{19}N_5O_4$: C, 59.84; H, 5.02; N, 18.36. Found: C, 59.61; H, 4.89; N, 18.16.

2,7-Diphenyl-1,8-octanedial (**69**).—To 20 mmol of the lithio salt of **19** was added 2.16 g (10 mmol) of 1,4-dibromopentane at −78°. After the usual isolation treatment, the bisoxazine was obtained (4.88 g) as a viscous oil. It was reduced without further purification with sodium borohydride (general procedure) using twice the normal quantity of hydride but not increasing the amount of solvent. Isolation gave 4.96 g of the tetrahydro oxazine, which was heated in the oxalic acid solution for 1.5 hr. The crude aldehyde, recovered by extraction and recrystallized from pentane, afforded 1.2 g of the aldehyde: mp 37–39°; 2,4-DNP mp 210–213°; nmr ($CDCl_3$) δ 10.4 (d, 2), 7.3 (m, 10), 3.4 (t, 2), 1–2.2 (m, 8); ir (neat) 2700, 1715 cm^{-1}.

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.47; H, 7.40.

1,2-Bis(dihydro-1,3-oxazinyl)ethane (**71**).—To a solution containing 30 mmol of the lithio salt of **18** at −78° was added rapidly 2.9 g (15 mmol) of 1,2-dibromoethane. After warming to room temperature, quenching, and extraction, there was formed 4.35 g of crude **71**. Distillation, bp 95° (0.1 mm), gave 3.90 g: ir (neat) 1660 cm^{-1}; nmr (CCl_4) δ 4.0 (m, 2), 2.25 (s, 4), 1.55 (t of d, 4), 1.25 (d, 6), 1.08 (s, 12). The product crystallized on standing, mp 43–44°.

Anal. Calcd for $C_{16}H_{28}N_2O_2$: C, 68.53; H, 10.06; N, 9.99. Found: C, 68.28; H, 10.22; N, 9.89.

4-Ethoxybutanal (**75**, **R = Et**).—The anion of **18** (40 mmol) was treated with 1.0 equiv of ethylene oxide at −78° and allowed to warm to room temperature. After quenching, extraction, and concentration, there was obtained 7.15 g (97%) of 2-(3-hydroxypropyl)oxazine (**73**, A = R = H): ir (neat) 1658, 3500 cm^{-1}; nmr ($CDCl_3$) δ 5.4 (s, 1, exchanges with D_2O), 4.1 (m, 1), 3.6 (t, 2). This product, without further purification, was treated in dry THF with 1.1 equiv of sodium hydride at 25° and after hydrogen evolution had ceased (30 min), 1.1 equiv of ethyl iodide was added and stirring was continued for 3 hr. Aqueous treatment followed by ether extraction, drying, and concentration produced the 2-(4-ethoxypropyl) oxazine **73** (A = H, R = Et) in 97% yield: ir (neat) 1658 cm^{-1}; nmr (CCl_4) δ 4.1 (m, 1), 3.4 (m, 4). Reduction with sodium borohydride and oxalic acid cleavage gave 4-ethoxybutanal, 2,4-DNP mp 88–89° (lit.[51] mp 88–89°), in 54% yield. The product was identical with that prepared using **18** and 2-bromoethyl ether (Table VI, entry 7).

4-Benzoylbutanal (**75**, **R = PhCO**).—The procedure was the same as above except that 1.1 equiv of benzoyl chloride was added in place of ethyl iodide. The benzoate (**73**, A = H, R = PhCO) was obtained in 94% yield (14.1 g), ir (neat) 1650, 1700 cm^{-1}. Reduction was performed on 5.8 g (20 mmol) of the oxazine and this resulted in 5.76 g of crude tetrahydro derivative, ir (neat) 3300–3500, 1710 cm^{-1} (absorption at 1650 cm^{-1}

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(51) H. Adkins and G. Krsek, *J. Amer. Chem. Soc.*, **71**, 3051 (1949).

was totally absent). The oxalic acid hydrolysis was performed on 2.9 g (10 mmol) and after extraction with ether, 1.31 g (62%) of 4-benzoyloxybutanal was obtained: 2,4-DNP mp 103–105°; ir (neat) 2710, 1710–1730 cm^{-1}; nmr (CCl_4) δ 9.81 (t, 1), 8.0 (m, 2), 7.4 (m, 3), 4.3 (t, 2), 1.0–2.8 (m, 6).

Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.66; H, 6.01.

1-Deuterio-2-phenyl-4-pentenal (Table VI, Entry 20) was prepared using 21.7 g (100 mmol) of the 2-benzyloxazine **19**, 48 ml (110 mmol) of *n*-butyllithium, and 12.1 g (100 mmol) of allyl bromide according to the general procedure for alkylation. The alkylated oxazine (21.0 g, 80 mmol) thus prepared was reduced with 3.7 g (95 mmol) of sodium borodeuteride (Merck) at −40° in THF–ethanol. The reduced oxazine was cleaved in aqueous oxalic acid after heating to reflux for 2 hr and the aldehyde was removed by ether extraction. A fractionally distilled product weighed 8.5 g: bp 64–65° (3 mm); ir (neat) 2580 (CD), 1705, 1640 cm^{-1}; nmr (CCl_4) δ 7.0–7.5 (m, 5), 4.8–6.0 (m, 3), 3.5 (t, 1), 2.0–3.1 (m, 2); 2,4-DNP mp 100–103°.

Anal. Calcd for $C_{11}H_{11}DO$: C, 81.95; H, 8.12. Found: C, 81.91; H, 8.12.

Addition of *n*-Butylmagnesium Bromide and Methyl Iodide to the 2-Vinyldihydro-1,3-oxazine (21). Formation of 85 (R = *n*-Butyl).—A solution of *n*-butylmagnesium bromide [from 82.2 g (0.6 mol) of *n*-butyl bromide and 15.3 g (0.63 g-atom) of magnesium] in 300 ml of tetrahydrofuran was added dropwise to a solution of 30.6 g (0.2 mol) of 2-vinyl oxazine **21** and 42.7 g (0.3 mol) of methyl iodide in 300 ml of tetrahydrofuran previously cooled in a Dry Ice–acetone bath (−60°). The resulting mixture was then allowed to warm to ambient temperature and stir overnight, after which it was treated carefully with water to decompose the excess Grignard reagent. The contents of the flask were poured into 1 l. of an ice–water mixture and acidified with dilute hydrochloric acid (6 *N*). The aqueous mixture was extracted with petroleum ether (bp 30–60°) and the extracts were discarded. The aqueous solution was rendered alkaline by addition of 35% sodium hydroxide solution and the resulting oil was collected and concentrated by ether extraction after drying with potassium carbonate. There remained 42 g (93%) of crude residue which after distillation, bp 59–61° (0.4 mm), gave 38.5 g (85%) of pure alkylated oxazine, **85** (R = *n*-butyl): ir (neat) 1650 cm^{-1}; nmr ($CDCl_3$) δ 4.0–4.3 (m, 1).

Anal. Calcd for $C_{14}H_{27}NO$: C, 74.61; H, 12.08; N, 6.21. Found: C, 74.47; H, 12.04; N, 6.27.

2-Methyl-3-phenylpropanal (Table X, Entry 1).—Utilizing the procedure described above for **85**, addition of phenylmagnesium bromide in ether (0.16 mol in 45 ml) to a solution of **21** (0.06 mol) and methyl iodide (0.09 mol) in 100 ml of tetrahydrofuran at −60 to −65° gave 14.8 g (93%) of crude dialkylated oxazine **85** (R = phenyl). Without further purification, the oxazine was reduced according to the general procedure using 2.5 g (0.06 mol) of sodium borohydride and this led to 13.7 g of tetrahydro-1,3-oxazine which was directly cleaved by addition to a boiling solution of oxalic acid (33 g per 150 ml of water) and collecting the aldehyde in the stream distillate. The oil was removed and concentrated from an ether solution to give 6.0 g (66% overall from **21**): ir (neat) 2710, 1730 cm^{-1}; nmr ($CDCl_3$) δ 9.7 (d, 1); semicarbazone mp 122–123°.

Reaction of 2-Vinyloxazine (21) with Sodiomalonic Ester.—A solution of 3.95 g (26 mmol) of **21** in 5 ml of absolute ethanol was added to 9.9 g (65 mmol) of diethyl malonate containing 0.05 g of sodium ethoxide in 40 ml of ethanol. The mixture was heated to reflux for 4 hr, cooled, diluted with water, acidified (6 *N* HCl), and extracted. The ethereal extracts were discarded and the aqueous solution was made alkaline (35% NaOH). Extraction of the oil with ether, drying (K_2CO_3), and concentration left 5.93 g (73%) of the ester oxazine **83** [N = CH-(CO_2ET)]: ir (neat) 1740–1750 (br), 1660 cm^{-1}; nmr ($CDCl_3$) δ 4.2 (q, m, 5), 3.4 (t, 1), 2.2 (m, 4), 1.6 (d of t, 2), 1.3 (d, 3), 1.0–1.2 (m, 17). Distillation at 0.2 mm was performed by a bulb-to-bulb apparatus.

Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.47; H, 8.49; N, 4.40.

Reaction of Enamines with 2-Vinyldihydro-1,3-oxazine (87).—Pyrrolidine enamines of cyclopentanone and cyclohexanone were prepared from known procedures.[52] A solution of **21** and the pyrrolidine enamine of cyclopentanone in equivalent amounts (0.10 mol of each) in 125 ml of benzene were heated to reflux with azeotropic removal of water for 15 hr. Addition of 50 ml of water was followed by another 30 min of heating and the entire mixture was poured onto ice–water (300 ml) and acidified with 9 *N* hydrochloric acid. The aqueous benzene mixture was extracted twice with ether and the extracts were discarded. The aqueous phase was made basic with 40% sodium hydroxide solution and the resulting oil was removed by several ether extractions, dried over magnesium sulfate, and concentrated. The residual oil, 23 g (97%), was distilled bulb-to-bulb [bp 97–110° (0.2 mm), ir (neat) 1735, 1660 cm^{-1})] giving pure **87**.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.59; H, 9.60; N, 5.80.

In a similar manner, **21** was treated with the pyrrolidine enamine of cyclohexanone and **87** (cyclohexanone analog) was formed in 94% yield, ir (neat) 1705, 1658 cm^{-1}.

Anal. Calcd for $C_{15}H_{25}NO$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.84; H, 9.88; N, 5.46.

Ketalization of 87 to 89.—The procedure of Nielsen[53] was adopted in the following manner. A mixture of **87** (9.0 g, 38 mmol), 25 ml of ethylene glycol, and 100 ml of toluene was treated with 8.0 g of *p*-toluenesulfonic acid monohydrate and heated to reflux in the presence of a Dean–Stark trap. Since, in addition to water, ethylene glycol is also distilled out of the system, the reaction vessel was replenished with 25 ml of ethylene glycol after 24 hr. The azeotropic process was repeated for an additional 24 hr until no more ethylene glycol was collected in the trap. The flask was cooled, the contents were poured into cold 10% sodium carbonate solution, and the organic layer was extracted with ether, dried ($MgSO_4$), and concentrated using initially a water aspirator and finally a vacuum pump. The crude ketal **89** was devoid of any carbonyl stretching frequency and the yield was 10.0 g (93%). Distillation, bp 130–134° (2 mm), gave pure material, ir (neat) 1668 cm^{-1}.

Anal. Calcd for $C_{16}H_{27}NO_3$: C, 68.29; H, 9.67; N, 4.98. Found: C, 68.74; H, 9.53; N, 4.91.

Reduction of the Dihydro-1,3-oxazinylethylcyclopentanone (87) to 88.—The reduction using sodium borohydride was carried out according to the general procedure using 4.0 g (17 mmol) of **87** and 0.5 g (15 mmol) of sodium borohydride in 50 ml of tetrahydrofuran–ethanol (1:1). Isolation of **88** gave 3.8 g (93%) of an oil as a mixture of stereoisomers which were not separated, ir (neat), 3350 cm^{-1} (broad). No C=N absorption at 1660 cm^{-1} was evident.

Reduction of Dihydro-1,3-oxazine 89 to Tetrahydro-1,3-oxazine 90.—Reduction using sodium borohydride (0.8 g, 20 mmol) of dihydro-1,3-oxazine **89** (5.6 g, 20 mmol) in 120 ml of ethanol–tetrahydrofuran at −40° was done according to the general procedure. In this instance, the reaction mixture was stirred for only 5–10 min after completion of the borohydride addition. Isolation was performed in the usual manner leaving 5.4 g (96%) of **90** as an oil; ir (neat) showed only NH absorption at 3280 cm^{-1} and no absorption at 1660 cm^{-1}.

Registry No.—**18,** 26939-18-4; **19,** 26939-22-0; *endo*-**20,** 36867-19-3; *exo*-**20,** 36867-20-6; **21,** 23878-88-8; **22,** 36867-22-8; **28,** 36867-23-9; **30,** 36867-24-0; **30a,** 36867-25-1; **31,** 36867-26-2; **32,** 36867-27-3; **42,** 36867-28-4; **49,** 36867-29-5; **50,** 6728-31-0; **52,** 36867-30-8; **54,** 36867-31-9; **54** perchlorate salt, 36900-97-7; **55,** 13050-09-4; **56,** 36867-33-1; **57,** 1540-83-6; **57** 2,4-DNP, 26385-63-7; **58,** 36867-36-4; **59,** 29304-32-3; **60,** 29822-84-2; **61,** 36867-39-7; **62,** 36867-40-0; **63,** 36867-41-1; **65** (E = D), 24314-24-7; **66** (E = D), 29304-33-4; **67,** 29304-29-8; **67** 2,4-DNP, 29304-30-1; **69,** 31859-53-7; **69** 2,4-DNP, 29304-31-2; **71,** 36871-39-3; **73** (A = H, R = Et), 36871-40-6; **73** (A = H, R = PhCO), 36871-51-9; **74** (A = H, R = PhCO), 36871-52-0; **83** [N = CH-($CO_2Et)_2$], 36871-41-7; **85** (R = *n*-Bu), 36871-42-8; **87,** 36871-43-9; **87** cyclohexanone analog, 36871-44-0;

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88, 36871-45-1; 89, 36871-46-2; 90, 36871-47-3; 2-(3-hexenyl)-DHO, 36872-13-6; 2-(3-hexenyl)-THO, 3687-14-7; 2-(5-bromopentyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine, 36871-48-4; 2-(5-chloropentyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine, 36871-49-5; 2-(4-cyano-1-phenylbutyl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine, 36871-50-8.

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Reactions of α,β-Dibromo Oximes and Related Compounds with Nitrosyl Chloride[1]

EDWARD G. BOZZI, CHYNG-YANN SHIUE, AND LEALLYN B. CLAPP*

Metcalf Laboratories, Brown University, Providence, Rhode Island 02912

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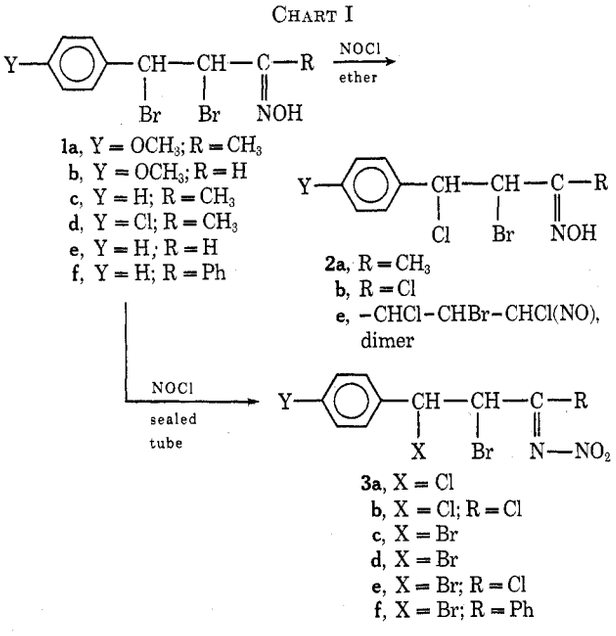
The reaction of nitrosyl chloride with α,β-dibromo oximes to give chloronitrimines consists of separate reactions even though the two reactions may occur in the same molecule. Replacement of bromine by chlorine is an SN1 reaction on the more activated secondary or on a tertiary bromine. Oxidation of the oximino function to a nitrimine occurs later in time and under more strenuous conditions in some cases, for example, in 1,2-dibromo-1-*p*-methoxyphenyl-3-butanone oxime. In other examples, the oxidation occurs without halogen displacement. In carvone oxime derivatives the replacement and oxidation occur in separated parts of the molecule.

Nitrosyl chloride[2] is known to react with aldoximes to give chloronitroso compounds, RCHClNO, or hydroxamic chlorides, ArCCl=NOH, or with ketoximes to give *gem*-chloronitroso compounds.[3] In an extension of the reaction to a series of α,β-dibromo ketoximes it was found that two reactions occurred: replacement of the α-bromine atom by chlorine and oxidation of the ketoxime to a nitrimine.[4] The reactions are not coupled; the present work shows that the replacement reaction is of SN1 character and that the oxidation is an independent reaction.

For example, 1,2-dibromo-1-*p*-methoxyphenyl-3-butanone oxime (**1a**) reacts with a slight excess of nitrosyl chloride in ether at 25° to replace the β-bromine with chlorine in 90% yield, without oxidizing the oxime, to give **2a** (Chart I). Longer treatment of **2a** with excess nitrosyl chloride or a sealed tube reaction gave the oxidized product **3a** in 46% yield. Direct treatment of **1a** with nitrosyl chloride in a sealed tube gave **3a** only. Apparently the *p*-methoxy group activates the benzylic position so that an SN1 type replacement occurs (see below).

The substituted dihydrocinnamaldoxime **1b** behaved similarly except that normal oxidation of the aldehydic hydrogen gave the hydroxamic chloride **2b**, which in turn was oxidized to the nitrimino chloride **3b**. In cases **1c–f** where the benzylic bromine was not activated by substitution on the aromatic ring, the oxidation reaction occurred without accompanying substitution with one exception. In the reaction of **1e** with nitrosyl chloride in ether, the 83% yield of α,β-dibromodihydrocinnamoyl hydroxamic chloride, a normal oxidation of the Rheinboldt type, was accompanied by a 12% yield of **2e**. However, in the sealed tube reaction a 94% yield of **3e** was obtained. Evidently under the more strenuous conditions of the sealed tube, oxidation of the aldoxime to nitrimino chloride was faster than substitution and the oxidation product was too unreactive for subsequent substitution. In ether the substitution and aldehydic oxidation reactions compete without the accompanying oxime oxidation.

CHART I



In the reaction of **1f**, the 70% yield of **3f** was accompanied by a 26% yield of 1-chloro-1-nitro-1,3-diphenylpropene (**5f**), suggesting that **4f** is an intermediate which is oxidized to **4g**. It was found recently[5] that aliphatic chloronitroso compounds are oxidized to chloronitro compounds by nitrosyl chloride, whereas after isomerization to the isomeric oximes, the oxidation produces only nitrimines, the main product in this case also. Loss of bromine to give the final product, **5f**, was not expected; none of the compounds **3c–e** behaved in that way even though these anticipated unsaturated compounds would be stabilized by more extensive conjugation than **5f**.

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