β-CHLOROVINYL KETONES

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Received December 4, 1964

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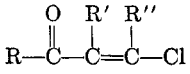
I. INTRODUCTION

β-Chlorovinyl ketones constitute a class of compounds which have served as useful intermediates for the synthesis of quite a variety of compounds. This review concerns compounds which have the general structure



in which R represents an alkyl or aryl group, but not hydrogen, while R′ and R″ may represent a hydrogen atom, an alkyl or aryl group, or a halogen atom. Because of the easy accessibility and high reactivity of compounds of the type RCOCH=CHCl, these compounds have been used as intermediates in the synthesis of a large variety of aliphatic, aromatic, and heterocyclic compounds; consequently, special emphasis is placed on the reactions of this particular type of β-chlorovinyl ketone. Vinyl ketones in which substitution occurs α and β in addition to the β-chlorine substituent have been less widely studied.

An effort has been made to include the references on β-chlorovinyl ketones through May 1964.

II. KETONES: TYPE RCOCH=CHCl

A. PREPARATION

1. *From Acetylene*

β-Chlorovinyl ketones having the general formula RCOCH=CHCl have been prepared in a wide variety of ways (see Table I). Perhaps the best method, and the one most often used, involves the addition of acid

$$RCOCl + HC{\equiv}CH \xrightarrow[CCl_4]{AlCl_3} RCOCH{=}CHCl$$

chlorides to acetylene in the presence of a Friedel–Crafts catalyst. The yields of β-chlorovinyl ketones prepared in this way (method A, Table I) are usually 70–80% depending on the conditions used, *i.e.*, temperature, solvent, catalyst, etc.

(1) Food and Drug Administration, Bureau of Scientific Research, Division of Food Chemistry, Washington 25, D. C.

TABLE I

β-CHLOROVINYL KETONES: RCOCH=CH—Cl

R	Method[a]	Bp (mm), °C [mp, °C]	% yield	n_D (°C)	d (°C)	Ref
CH_3	A	40–41 (24)	62	1.4654 (20)	1.130 (20)	196; 2 (A), 9 (B), 28 (B), 32 (A), 75 (B), 163 (A), 170 (A), 222 (A), 224 (D), 225 (A), 226 (A), 227 (E)
	cis isomer	43.5–46.5 (20)	38.9	1.4630 (20)	1.1234 (20)	61
	trans isomer	75.5–78.5 (100)	50	1.4670 (20)	1.1240 (20)	
C_2H_5	A	55–56 (27)	47	1.4596 (23)	1.0702 (23)	170, 2 (A), 75 (B), 150 (B), 227 (E)
n-C_3H_7	A	56–57 (12)	74.5	1.4640 (23)	1.0396 (23)	170, 75 (B), 227 (E)
i-C_3H_7	A	50–51 (12)	63.3	1.4585 (20)	1.0317 (20)	78, 189 (A)
i-C_4H_9	A	64–65 (12)	72	1.4590 (20)	1.0117 (20)	170, 9 (B), 57 (A), 75 (B), 163 (A), 195 (A), 222 (A)
t-C_4H_9	C	66–67.5 (27)	73	1.4593 (20)	1.0031 (20)	87
n-C_5H_{11}	B	76–77 (7)	59.9	1.4620 (20)	1.0157 (20)	75, 222 (A)
i-C_5H_{11}	A	108 (30)	65	1.4619 (20)	0.993 (20)	196
n-C_6H_{13}	A	90–93 (4.5)	75	1.4646 (21)	0.9871 (21)	222
i-C_6H_{13}	A	64 (1)	80	1.4600 (20)	0.975 (20)	196
n-C_7H_{15}	A	111–113 (5) [22–22.5]	74	1.4632 (21)	0.9733 (21)	221, 222 (A)
n-C_8H_{17}	A	125–127 (4) [20–21]	77	1.4562 (21)	0.9695 (21)	222
n-C_9H_{19}	A	131–134 (4) [35–35.5]	58	...	...	222
n-$C_{10}H_{21}$	A	131–134 (4) [32–32.5]	54	...	...	222
n-$C_{11}H_{23}$	A	[44–44.5]	61	...	...	222
n-$C_{12}H_{25}$	A	[41–42]	68	...	...	222
n-$C_{13}H_{27}$	A	[53.5–54]	64	...	...	222
n-$C_{15}H_{31}$	A	[60.5–61]	67	...	...	221, 222 (A)
n-$C_{16}H_{35}$	A	...	..	...	...	163
CH_2=CH–	A	48–49.5 (14)	31.5	1.4938 (20)	1.1274 (20)	111
CH_3CH=CH–	A	70–72 (10) [38–39]	47.3	...	...	111
$(CH_3)_2C$=CH	A	71–73 (10)	34	1.5038 (20)	1.0644 (20)	111
$C_2H_5O_2C(CH_2)_4$–	A	...	..	...	...	209
$ClCH_2$–	A	71–72.5 (11)	..	1.5079 (20)	1.3486 (20)	225, 28 (B), 121 (A)
Cl_3C	...	75–76 (12)	..	1.5076 (25)	1.5321 (25)	199
$Cl(CH_2)_2$–	A	100–101 (15–16)	..	1.5002 (20)	1.2862 (20)	225, 57 (A), 111 (A), 163 (A)
$CH_3CH(Cl)$–	A	69–70 (11)	55	1.4960 (20)	1.2640 (20)	109
$C_6H_4CH_2$	A	...	..	...	...	222
C_6H_5	A	92–96 (2)	65–70	1.5860 (20)	1.2062 (20)	112, 2 (C), 9 (B), 75 (B), 175 (C), 190 (C), 222 (A)
o-$CH_3C_6H_4$	A	105–107 (4)	66	1.5733 (20)	1.1612 (20)	131
m-$CH_3C_6H_4$	A	101–103 (2) [14–15]	55.7	1.5772 (20)	1.1529 (20)	131
p-$CH_3C_6H_4$	A	123–127 (5)	70–75	1.5835 (20)	1.1693 (20)	112, 194 (C)
o-BrC_6H_4	A	118–122 (1.5–2) [45.5–46.5]	56–62	...	...	112, 75 (B)
p-BrC_6H_4	A	135–138 (3) [36–37]	77	...	...	131, 175 (C)
o-ClC_6H_4	A	145–146 (15) [41–43]	65	...	...	106, 30
p-ClC_6H_4	A	114–116 (2) [35.5–36]	59	...	...	112, 30
2,4-$Cl_2C_6H_3$	...	[7]	..	...	...	30
2,4,5-$Cl_3C_6H_2$	...	[92]	..	...	...	30
m-$NO_2C_6H_4$	A	[72]	31	...	...	106
p-$NO_2C_6H_4$	A	[88.5–89]	57.5–60	...	...	112, 30, 75 (B)
p-$CH_3OC_6H_4$	C	154–157 (3) [47–48]	60	...	...	175, 75 (B)
C_4H_3O	A	102–105 (10) [46–48]	41	...	...	126
C_4H_3S	A	154–156.5 (23) [25.5–27]	65	...	...	126
C_4H_3Se	A	133–134 (7)	45	1.6540 (20)	1.6621 (20)	126

[a] Method A, acid chloride + acetylene; B, acid chloride + vinyl chloride; C, hydroxymethylene ketone + thionyl chloride; D, acid chloride + vinylidene chloride followed by treatment with zinc; E, silico anhydride + acetylene. [b] The data given in the table for each compound are from the first reference listed since several citations are often shown. The capital letters indicate the method in that reference.

This process has been the subject of several patents (57, 151, 162, 163) using a wide variety of catalysts ($SnCl_2$, $ZnBr_2$, $AlCl_3$, $SbCl_5$, etc.) and solvent systems ($CHCl_3$, CCl_4, CS_2, CH_2Cl_2, etc.). Apparently with aliphatic acyl halides the reaction is carried out best by preparing a solution of the acyl halide and aluminum chloride in carbon tetrachloride and then introducing the acetylene at 0–10° over a period of several hours

(170) or until rapid absorption of acetylene ceases (196). Under these conditions, however, benzoyl chloride fails to condense. In the case of aromatic acid halides, best results are obtained when the $AlCl_3$–ArCOCl complex is prepared in advance at low temperatures (<10°) in 1,2-dichloroethane and then the acetylene is added at 40–50° for 6–7 hr. In this way, yields of 60–70% of chlorovinyl ketones are obtained regularly (112).

Heterocyclic acid chlorides (from 2-furoic, thiophene-2-carboxylic, and selenophene-2-carboxylic acids) also react, but at somewhat elevated temperatures (30–40°) (126).

α,β-Unsaturated acid halides react with acetylene at 0–10° to form alkenyl β-chlorovinyl ketones (111). These compounds also may be prepared from the more accessible α- or β-halo acid chlorides. In the latter case the initially formed haloalkyl β-chlorovinyl ketone may be dehydrohalogenated with diethylaniline.

$$RCH_2\underset{\displaystyle Cl}{\underset{|}{C}}H{-}COCl + H{-}C{\equiv}CH \rightarrow RCH_2\underset{\displaystyle Cl}{\underset{|}{C}}H{-}COCH{=}CHCl \xrightarrow{C_6H_5N(C_2H_5)_2} RCH{=}CHCO{-}CH{=}CHCl$$

2. *From Vinyl Chloride*

A second method of synthesis of β-chlorovinyl ketones which has been used quite frequently involves the addition of acid chlorides to vinyl chloride in the presence of a Friedel–Crafts catalyst. This method also has

$$RCOCl + H_2C{=}CHCl \longrightarrow RCOCH_2CHCl_2 \xrightarrow{-HCl} RCOCH{=}CHCl$$

been the subject of several patents (9, 57) and has the obvious disadvantage of being a two-step procedure involving the elimination of hydrogen chloride, which could catalyze the polymerization of the β-chlorovinyl ketone. The intermediate β,β-dichloroethyl ketones have been isolated and characterized in some cases, but normally they spontaneously eliminate hydrogen chloride on standing (75). The structure of the dichloro ketone intermediate was investigated (28), and it was found that the intermediate is not the α,β-dichloroethyl ketone prepared by chlorination of the corresponding unsaturated ketone, and therefore must be the isomeric β,β-dichloroethyl ketone (see above).

In the case of aliphatic acid halides, the best procedure appears to be the addition of vinyl chloride at 20–25° to a slurry of aluminum chloride and the acid chloride in chloroform over a period of 1–2 hr. Hydrolysis with ice and treatment of the chloroform solution of the β,β-dichloroethyl ketone with aqueous sodium bicarbonate (at reflux for 4–5 hr) gave yields of 50–84% of the β-chlorovinyl ketone (75).

Aromatic acid halides react similarly, but the intermediate β,β-dichloroethyl ketones apparently are much more stable. In the patent literature the condensation of benzoyl chloride with vinyl chloride is described (9), but the method was found to be unsatisfactory by later workers (175, 190), since difficultly separable mixtures of the β-chlorovinyl and β,β-dichloroethyl ketones were obtained. However, reinvestigation of the problem revealed that further treatment of the reaction mixtures with the requisite amount of triethylamine resulted in good yields of the expected aryl β-chlorovinyl ketones. In the case of *p*-methoxybenzoyl chloride, it was found necessary to change the solvent to nitromethane (75).

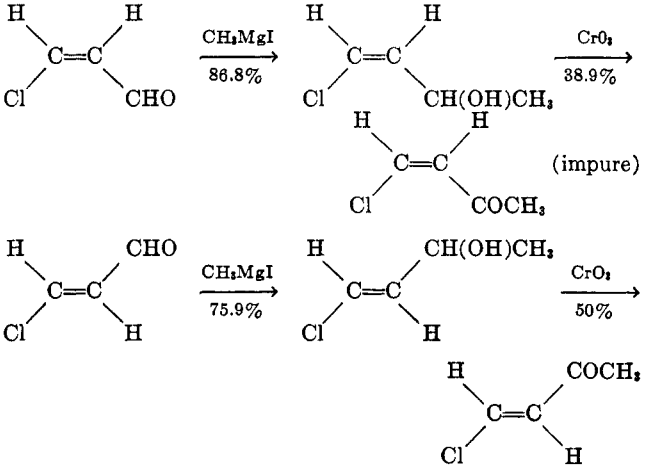
3. *From Hydroxymethylene Ketones*

A third method of obtaining β-chlorovinyl ketones, which has been used frequently, involves the reaction of thionyl chloride with hydroxymethylene ketones or their sodium salts (175). This is the method of choice where R is *t*-butyl, since in the presence of aluminum chloride, pivalyl chloride appears to isomerize, so that in both of the previous methods a large number of inseparable side products form (87). This procedure has two disadvantages: (a) the formylation of unsymmetrical ketones usually leads to mixtures of products, and (b) the necessary substituted acetophenones are not readily available.

$$RCOCH{=}CHOH + SOCl_2 \rightarrow RCOCH{=}CHCl + SO_2 + HCl$$

4. *Miscellaneous Methods*

Of special interest is the recent work of Ivanov and collaborators (61) who prepared both the *cis*- and *trans*-methyl β-chlorovinyl ketones *via* the following reaction paths.

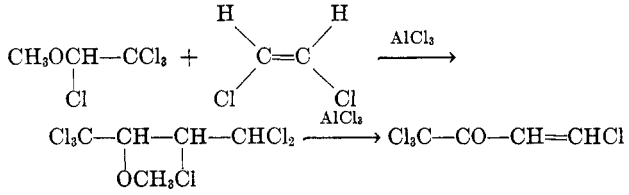


Another method of synthesis described in the literature involves the addition of acid anhydrides to acetylene in the presence of a Friedel–Crafts condensing agent (226).

The addition of silico anhydrides (tetraalkoxysilanes) to acetylene in the presence of aluminum chloride gave 30–41% yields of β-chlorovinyl ketones (227).

$$Si(OCOR)_4 + 4HC{\equiv}CH \xrightarrow{AlCl_3} [Si(O{-}CH{=}CH{-}COR)_4] \xrightarrow{AlCl_3} 4RCOCH{=}CHCl + Si(OAlCl_2)_4$$

Prins and Haring (199) prepared trichloromethyl β-chlorovinyl ketone through condensation of methyl α, β,β,β-tetrachloroethyl ether with *cis*-1,2-dichloroethylene in the presence of aluminum chloride.

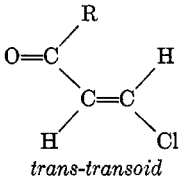


Finally, Wichterle and Vogel (224) prepared methyl β-chlorovinyl ketone by treating methyl β,β-dichlorovinyl ketone with zinc dust in ethanol, while Petrov and Sopov (191) treated 1-chloro-3-methoxy-1,3-butadiene with 5% sulfuric acid to obtain the same product. In each of these cases the starting materials are not readily available.

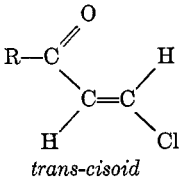
B. PHYSICAL PROPERTIES AND STRUCTURES

β-Chlorovinyl ketones are high-boiling liquids or low-melting solids. The lower boiling members of this class of compounds are highly lachrymatory and strongly vesicant. The aromatic β-chlorovinyl ketones are considerably more stable than their aliphatic counterparts. Methyl β-chlorovinyl ketone is quite unstable; when prepared from acetylene it turns dark brown when kept at −20° for about 1 month, but may be redistilled to again give the colorless ketone. If prepared from vinyl chloride, however, this compound will decompose almost explosively within 1 day, producing large volumes of hydrogen chloride and leaving a hard, black polymer. On the other hand, phenyl β-chlorovinyl ketone from acetylene is stable at room temperature almost indefinitely. These β-chlorovinyl ketones may be stabilized by addition of 0.5% phenol or hydroquinone (144). The alkenyl β-chlorovinyl ketones appear to be least stable, but may be kept several days in cold ether in the presence of hydroquinone or in the absence of light (111).

Several studies have shown that β-chlorovinyl ketones prepared from acetylene have the *trans* configuration. Thus proton magnetic resonance spectra showed that these compounds are not less than 95% *trans* with coupling constants of the two vinylic hydrogens being 13–14 cps (18). An investigation of the infrared and ultraviolet spectra also indicated not only a *trans* configuration, but also a *transoid* conformation (18). Thus a series of alkyl β-chlorovinyl ketones has been found to absorb maximally in 95% ethanol in the 229–232.5-mμ (ε 11,200–14,600) region indicating considerable conjugation and a planar structure. Methyl β-chlorovinyl ketone absorbs maximally at 229 mμ (ε 14,600). In comparison, a fixed *transoid* β-chlorovinyl ketone, *i.e.*, 3-chloro-5,5-dimethyl-2-cyclohexen-1-one, absorbs maximally at 238 mμ (ε 13,500). The infrared spectra of these compounds indicated a conjugated system, the carbonyl absorption lying in the 1678–1698-cm^{-1} region, and the double bond absorption being found in the 1582–1592-cm^{-1} region. Bands are found also in the 941-cm^{-1} region indicating the presence of *trans*-vinyl protons. Phenyl β-chlorovinyl ketone absorbs maximally in the ultraviolet region at 203 (ε 10,400) and 260 (ε 16,500) mμ. As chemical evidence for the *trans* configuration, methyl β-chlorovinyl ketone has been oxidized under carefully controlled conditions to *trans*-β-chloroacrylic acid; no *cis* acid could be detected (69, 99).



trans-transoid



trans-cisoid

In the case of the addition of acid chlorides to vinyl chloride, however, the evidence, which is not conclusive, indicates that on elimination of hydrogen chloride from the β,β-dichloroethyl ketone intermediate, both *cis*- and *trans*-β-chlorovinyl ketones form. Since, in the *cis* form, ready *trans* elimination of hydrogen chloride may occur, and since hydrogen chloride appears to catalyze the polymerization of β-chlorovinyl ketones, the greater instability of these mixtures of compounds is predictable. In none of the other methods has the configuration of the product been established definitely.

C. CHEMICAL TRANSFORMATIONS

The chemistry of β-chlorovinyl ketones resolves itself into three general reaction classes: (1) additions to the carbonyl group; (2) additions to the double bond; and (3) additions to the β position, followed by replacement of the β chlorine by a large and varied group of nucleophiles.

1. *Additions to the Carbonyl Group*

In this category are found the addition of Grignard reagents and sodium alkyls to form the corresponding carbinols in good yields (see Table II). No 1,4-addition products have been observed, but only a limited number of compounds have been investigated. These compounds are of considerable interest, because they

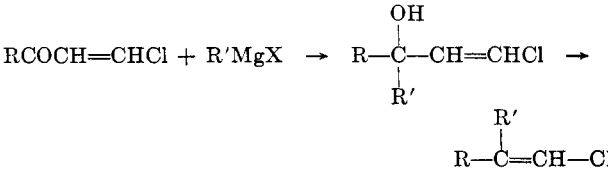
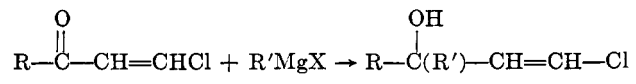
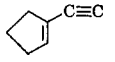
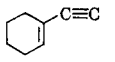
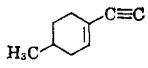
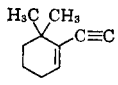
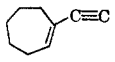


TABLE II

REACTION OF β-CHLOROVINYL KETONES WITH GRIGNARD REAGENTS



R	R′	% yield of product	Bp (mm), °C	n_D (°C)	Ref
CH_3	CH_3	51	80 (18)	1.4580 (19)	66
CH_3	C_6H_5	56	108–110 (3)	1.5690 (18)	66
CH_3	HC≡C	55	68 (16)	1.4780 (20)	66
CH_3	n-C_4H_9C≡C	95	77–78.5 (0.3)	1.4818 (17)	65
CH_3	H_2C=CH—C≡C	85	78 (1)	1.5168 (17)	65
CH_3		70	65–70[a] (10^{-4})	1.5398 (15)	26
CH_3		87	65[a] (10^{-4})	1.5354 (21)	219
CH_3		98	50–55[a] (10^{-5})	1.5228 (17)	219
CH_3		95	75–80[a] (10^{-4})	1.5232 (23)	219
CH_3		85	80–85[a] (10^{-4})	1.5372 (18)	26

[a] Bath temperature.

rearrange under the influence of dilute sulfuric acid to α,β-unsaturated aldehydes (26, 47, 65, 67, 219).

The carbonyl group of β-chlorovinyl ketones is easily reduced with lithium aluminum hydride to the corresponding carbinol (see Table III). Hydrogenation over Raney nickel or with 10% palladium on carbon reduces both the carbonyl group and the double bond (41).

Several attempts have been made to prepare carbonyl derivatives of β-chlorovinyl ketones. Both aliphatic (170) and aromatic (106) β-chlorovinyl ketones react readily with phenylhydrazine to form 1-phenyl-3-alkyl-(aryl)pyrazoles (see Table IV). This synthesis of pyrazoles is of considerable utility, since the one other method of preparation—the reaction between hydroxymethyleneacetophenones often yields mixtures of both the 1,3- and 1,5-disubstituted pyrazoles. The initial products, the phenylhydrazones, have not been isolated. However, *p*-nitrophenylhydrazine does react rapidly with methyl β-chlorovinyl ketone at room temperature to form the *p*-nitrophenylhydrazone which is quantitatively cyclized by boiling in acetic acid for 1–2 min or simply by fusion of the solid *p*-nitrophenylhydrazone (106).

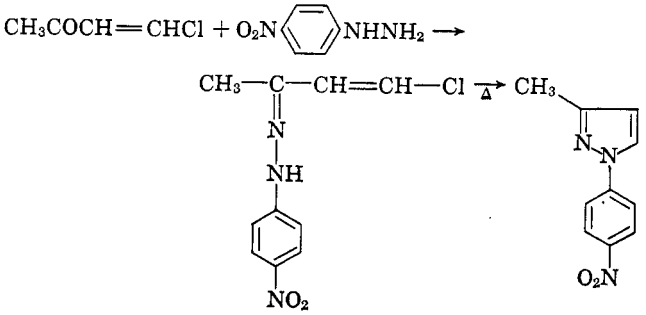
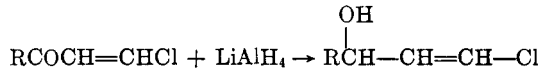


TABLE III

REACTIONS WITH LITHIUM ALUMINUM HYDRIDE (41)

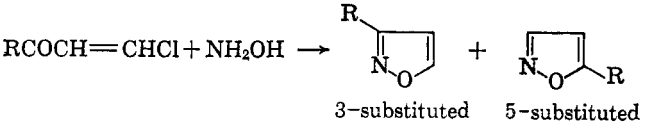


R	% yield	Bp (mm), °C	$n^{20}D$	Phenylurethan Mp, °C
C_2H_5	..	71 (25)	1.4621	88–89
n-C_3H_7	88	84 (15)	1.4617	67–68
i-C_4H_9	73	92 (18)	1.4595	...
n-C_5H_{11}	84	80 (1.2)	1.4628	67–68
n-C_6H_{13}	68	73–74 (0.08)	1.4627	75

The 2,4-dinitrophenylhydrazones of isoamyl and isohexyl β-chlorovinyl ketones have also been prepared, having melting points of 118–119° and 112–112.5°, respectively (196).

Hydrazine hydrate reacts similarly; simply heating an equimolar mixture of hydrazine hydrate and β-chlorovinyl ketone in ether or acetic acid leads to good yields of 3-substituted pyrazoles (see Table IV). None of the 5-substituted isomers could be detected.

Normally, attempts to form the oximes of β-chlorovinyl ketones fail owing largely to the ease with which the β-chlorine atom is lost. However, this reaction between hydroxylamine and β-chlorovinyl ketones is one of the simplest methods known for the synthesis of isoxazoles (see Table V). Other types of β-chlorovinyl ketones actually form oximes (see later sections). In the case in which R is an alkyl group, the method is of little utility, since mixtures of 3- and 5-substituted isoxazoles form. The 3-substituted isomer of course results through initial addition to the carbonyl group followed by cyclization; whereas the 5-substituted isoxazole is a result of initial displacement of the β-chlorine



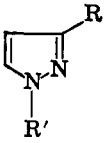
3-substituted 5-substituted

atom, which is an extremely facile process. Physical separation of these isomers is very difficult and is sometimes impossible (121). However, if the carbonyl is activated, as in chloromethyl β-chlorovinyl ketone, then only the 3-substituted isomer forms (109, 121). Phenyl β-chlorovinyl ketone also yields mixtures (62–67% of the 3-phenyl isomer) of isoxazoles. However, phenyl β-chlorovinyl ketones substituted in the aromatic nucleus (*p*-methyl, *p*-chloro, etc.) react to form only 5-substituted isoxazoles in yields of 70–90%; consequently, this probably represents the most convenient synthesis of these compounds (106).

Finally, semicarbazide, which is much less basic than hydroxylamine (63), has been reported by Cornillot

TABLE IV

3-ALKYLPYRAZOLES FROM β-CHLOROVINYL KETONES



R	R′	Bp (mm), °C [mp, °C]	n_D (°C)	d_4 (°C)	% yield	Ref
CH_3	H	204–206 (755)	1.4935 (14)	1.0206 (14)	61	170
C_2H_5	H	107–108 (15)	1.4934 (20)	0.9818 (20)	66.5	170
n-C_3H_7	H	225–226 (750)	1.4875 (20)	0.9697 (20)	64.5	170
i-C_4H_9	H	230–231 (754)	1.4818 (20)	0.9455 (20)	69	170
t-C_4H_9	H	214–215 (748) [48–51]	1.4825 (26)	...	73	87
C_6H_5	H	[76.5–77]	...	...	84	106
o-BrC_6H_4	H	[127]	...	...	71	106
o-ClC_6H_4	H	[89–90]	...	...	98	106
p-ClC_6H_4	H	[98]	...	...	79	106
m-$NO_2C_6H_4$	H	[120]	...	...	93	106
p-$NO_2C_6H_4$	H	[192]	...	...	85	106
CH_3	C_6H_5	255–256 (752)	...	...	42	170
CH_3	p-BrC_6H_4	[93.5–94]	...	...	79	170
CH_3	p-$NO_2C_6H_4$	[165.5–166]	...	...	84	170
C_2H_5	p-$NO_2C_6H_4$	[122–22.5]	...	...	84	170
n-C_3H_7	p-$NO_2C_6H_4$	[104.5–105]	...	...	69	170
i-C_4H_9	p-$NO_2C_6H_4$	[65–66]	...	...	65	
CCl_3	C_6H_5	145–147 (0.1) [85–86]	...	...	...	200
C_6H_5	C_6H_5	[83–84.5]	...	...	57	106
p-$NO_2C_6H_4$	C_6H_5	[136]	...	...	64	106
p-ClC_6H_4	C_6H_5	[118]	...	...	75	106
C_6H_5	p-$NO_2C_6H_4$	[169]	...	...	63	106
C_4H_3O	p-$NO_2C_6H_4$	[70.5–72]	...	...	62	126
C_4H_3Se	p-$NO_2C_6H_4$	[100–101]	...	...	63	126

TABLE V

ISOXAZOLES FROM β-CHLOROVINYL KETONES

R	% yield (mixture)	Bp (mm), °C [mp, °C] (mixture)	$n^{20}D$ (mixture)	d^{20}_4 (mixture)	% 3-R isomer	% 5-R isomer	Ref
CH_3	58.4	118–122	1.4380	1.0283	23	77	121, 165
C_2H_5	60	139–140	1.4440	0.9916	59	41	121
n-C_3H_7	73	160–161	1.4468	0.9722	67	33	121
i-C_4H_9	70	168–169	1.4480	0.9450			121
$ClCH_2$	85	65–66 (20)	1.4810	1.2745	90	10	121
C_6H_5	70–80	91–93 (3)	1.5826	...	67	33	105
p-$CH_3C_6H_4$	90	[58–60]	...	...		100	105
p-ClC_6H_4	90	[82–82.5]	...	...		100	105
p-$NO_2C_6H_4$	70	[172–174]	...	...		100	105
$CH_3CH(Cl)$	86	69–70 (20)	1.4792	1.1869	97	3	109

and Alquier (32) to yield a semicarbazone with methyl β-chlorovinyl ketone, mp 180°. Yakabovich and Merkulova (225), however, report a melting point for the same compound of 118–119°. These authors also report semicarbazones for chloromethyl (mp 124–125°) and β-chloroethyl β-chlorovinyl ketone (mp 160–170° dec). In addition, a semicarbazone, mp 101–104°, has been reported for ethyl β-chlorovinyl ketone (43).

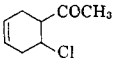
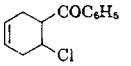
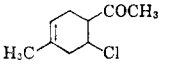
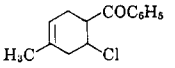
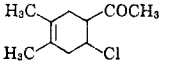
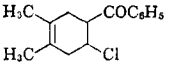
2. *Additions to the Double Bond*

In this second category is found the addition of various dienes to β-chlorovinyl ketones to form the corresponding Diels–Alder adducts (Table VI). The true configuration of these adducts apparently has not been established definitely. The reaction between alkyl β-chlorovinyl ketones and cyclopentadiene is spontaneous without solvent and is complete within 10–15 min. The usefulness of this reaction in organic synthesis is illustrated in Scheme I (108,110).

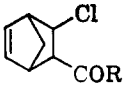
In the case of vinyl β-chlorovinyl ketone, cyclopentadiene in excess reacts to form the bis adduct; however, if a mole ratio of 1:1 is used, then reaction occurs preferentially at the vinyl group (95). Thus the β-chlorovinyl group exhibits the lesser dienophilic ac-

Table VI

Diels–Alder Adducts

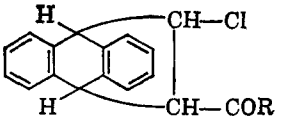
Dienophile RCOCH=CHCl R	Diene	Product	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3			85–86 (6)	1.4960	1.074	60	84
C_6H_5			148–150 (1)	1.5670	1.1620	50	84
CH_3			118–120 (10)	1.5010	1.0690	57	84
C_6H_5			[76]	...	...	61	84
CH_3			[35]	...	...	43	84
C_6H_5			[62]	...	...	71	84

Diels–Alder Adducts with Cyclopentadiene



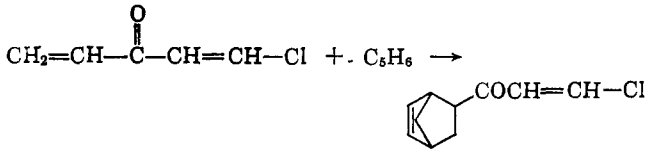
R	Bp (mm), °C [mp, °C]	$n^{25}D$	d^{20}_4	% yield	Ref
CH_3	80–82 (5)	1.5016	1.5016	88	168
C_2H_5	91–94 (1)	1.4985	1.1322	91–96	76, 108
n-C_3H_7	98–100 (5)	1.4941	1.0918	86.6	168
n-C_5H_{11}	107–109 (2)	1.4920	1.0565	75	168
$ClCH_2$	116–118 (6) [62–63]	...	...	40	168
C_6H_5	[102]	...	...	70	168
p-$CH_3C_6H_4$	[91.5–92]	...	...	75	107
p-ClC_6H_4	[94.5–95]	...	...	80	107
p-$NO_2C_6H_4$	[147–48]	...	...	76	107
CH_2=CH	144.5–145 (4) [80–90] (diadduct)	...	...	74	95
CH_3CH=CH	107–109 (5)	1.5215	1.1456	40.5	95
$(CH_3)_2C$=CH	104–104.5 (5)	1.5223	1.1103	75	95

Diels–Alder Adducts with Anthracene



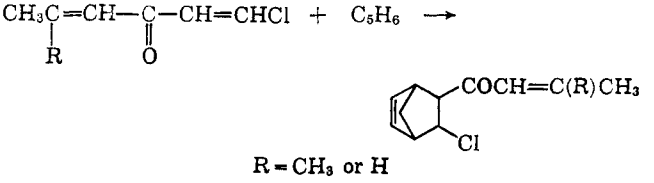
R	Mp, °C	% yield	Ref
CH_3	145	87.6	183
n-C_3H_7	93–94	84.4	183
n-C_5H_{11}	82	70.1	183
C_6H_5	184–186	80.6	183

tivity probably due to the deactivating influence of the chlorine atom on the double bond,  .



50.3%

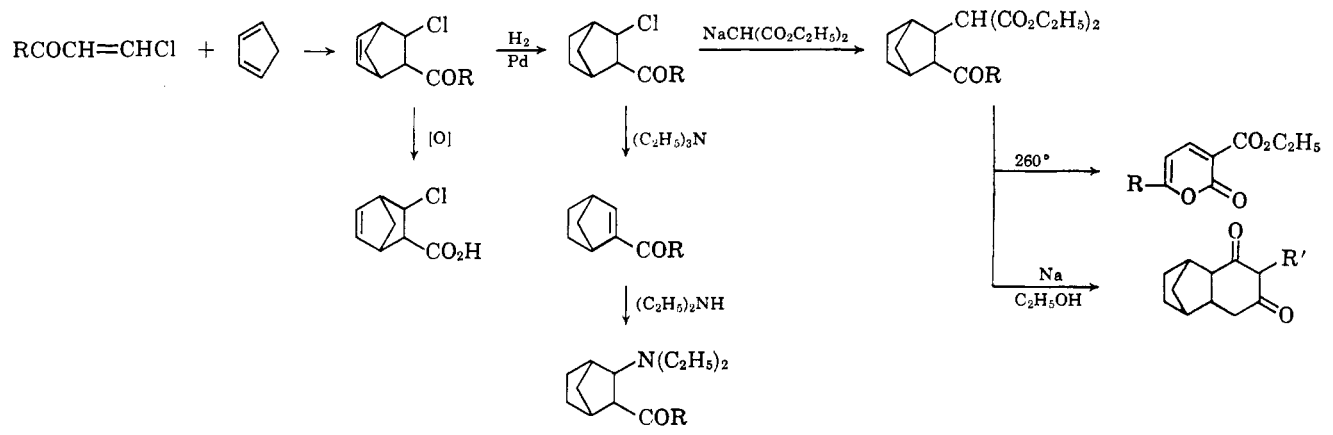
In the case of propenyl β-chlorovinyl ketone and isobutenyl β-chlorovinyl ketone, the β-chlorovinyl group reacts preferentially with cyclopentadiene (95).



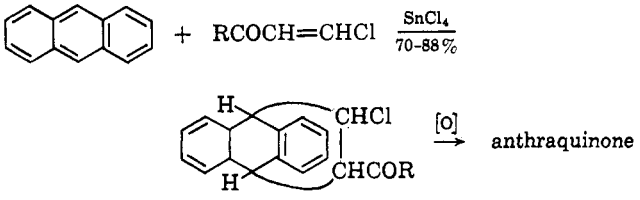
$R = CH_3$ or H

Anthracene does not react with β-chlorovinyl ketones in benzene even at elevated temperatures. However, if

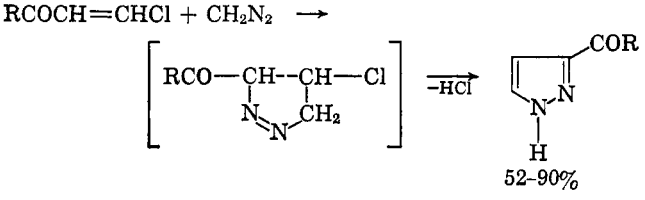
SCHEME I



the reaction is catalyzed with equimolar amounts of stannic chloride, ready condensation occurs (183) (Table VI).



Several diazo compounds react with the double bond of β-chlorovinyl ketones. Thus diazomethane in cold ether readily adds to the double bond forming an intermediate which loses the elements of hydrogen chloride forming 3-acylpyrazoles (Table VII) isolated as the hydrochlorides (86, 87, 165, 166). Ethyl diazoacetate



reacts similarly, forming 3-acyl-4-carbethoxypyrazoles (166), while diazo ketones lead to the formation of 3,5-diacylpyrazoles (85) (Table VII).

The condensation of β-chlorovinyl ketones with equimolar amounts of phenylazide in benzene also proceeds *via* preliminary addition to the double bond with subsequent loss of the elements of hydrogen chloride (82). However, in this case, due to the lower basicity of the triazoles formed, the hydrogen chloride released does not react to form the hydrochlorides. Conceivably this condensation could produce 1-phenyl-4-acyltriazoles or 1-phenyl-5-acyltriazoles; however, the only products isolated were the 1-phenyl-4-acyltriazoles (Table VIII).

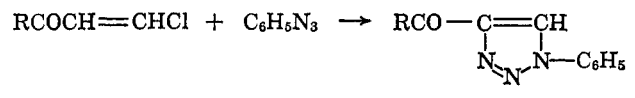


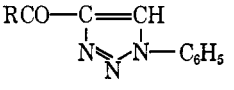
TABLE VII

PYRAZOLES FROM β-CHLOROVINYL KETONES

R	R′	Mp, °C	% yield	Ref
CH_3	H	100–101	67.5	165
C_2H_5	H	123–124	90	166
n-C_3H_7	H	104–105	71	166
i-C_4H_9	H	84–85	73	166
t-C_4H_9	H	99–100	51.5	87
C_6H_5	H	98–99	64	166
p-$CH_3OC_6H_4$	H	97–97.5	80	86
p-$CH_3C_6H_4$	H	134.5–135	75	86
p-ClC_6H_4	H	129–131	41	86
p-$NO_2C_6H_4$	H	187–187.5	56	86
CH_3	CO_2Et	112–112.5	34	166
CH_3	$COCH_3$	148–149.5	42	85
CH_3	COC_6H_5	125.5–126.5	52	85
CH_3	COC_2H_5	129.5–131	47	85
n-C_3H_7	$COCH_3$	108.5–110	33	85
t-C_4H_9	$COCH_3$	144–146	50	85
t-C_4H_9	COC_2H_5	113–115	50	85
t-C_4H_9	COC_6H_5	95.5–98.5	37	85
C_6H_5	$COCH_3$	125–126	62	85
C_6H_5	COC_2H_5	137–139	53	85
C_6H_5	COC_6H_5	150.5–152	81	85

TABLE VIII

1-PHENYL-4-ACYLTRIAZOLES FROM β-CHLOROVINYL KETONES

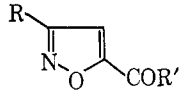


R	Mp, °C	% yield	Ref
CH_3	108–109	38	82, 165
n-C_3H_7	109–110	29.2	82
i-C_4H_9	90.5–91	21	82
$ClCH_2$	154–155	61	82

In an analogous way, nitrile oxides react readily with β-chlorovinyl ketones to form 3-alkyl-5-acylisoxazoles (42) (see Table IX).

TABLE IX

3-ALKYL-5-ACYLISOXAZOLES (42)



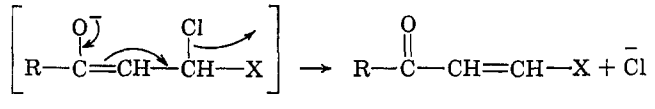
R	R′	Mp, °C	% yield
C_6H_5	CH_3	104.5	18.6
C_6H_5	C_2H_5	111–112	23.5
C_6H_5	n-C_3H_7	92–93	19.5
C_6H_5	i-C_4H_9	73–74	....
C_6H_5	n-C_5H_{11}	86–87	17.2
C_6H_5	n-C_6H_{13}	74–75	12.8
p-BrC_6H_4	n-C_3H_7	140–141	11.2

3. *Replacement of the β-Chloro Substituent*

This third class of reactions undergone by β-chlorovinyl ketones involves the replacement of the β-chlorine atom by a large variety of nucleophilic reagents. These reactions represent essentially a general method of introduction of the ketovinyl radical into a molecule of an organic compound, and consequently have been termed "ketovinylation" reactions (118).

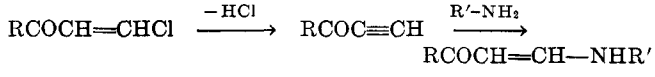
It is well known that vinylic halides are extremely resistant to nucleophilic replacement reactions. However, in cases in which the vinylic halide is activated by an electron-withdrawing group or a group which may stabilize a negative charge in the β position, replacement of the halide is known to occur quite readily (140, 142). Thus β-chloroacrylonitrile reacts readily with a large variety of nucleophiles forming the expected β-substituted acrylonitriles (213). The *cis*- and *trans*-β-chlorocrotonates (64) as well as the β-chlorocrotonic acids (3) similarly react with a number of nucleophilic reagents forming the expected β-substituted crotonates. These reactions were found to proceed largely with retention of configuration (147).

Several mechanisms by which the β-chlorine atom of β-chlorovinyl ketones may be replaced by nucleophilic reagents are possible. The most generally accepted mechanism is depicted as (64, 81, 193)



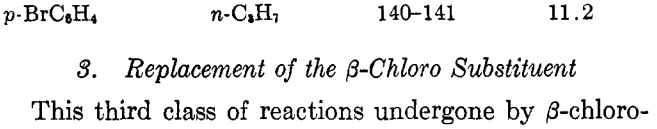
In this mechanism X^- represents the attacking nucleophile. Uncharged species (*i.e.*, amines) react analogously.

Two other mechanisms have been proposed (64, 193, 216). One involves preliminary elimination of hydrogen chloride to form an acetylenic ketone which then reacts further to form the products (an elimination–addition mechanism). Using a primary amine as the nucleophile this mechanism may be written as



This mechanism was thought to be unlikely on the basis that these reactions are kinetically very fast in most cases, and more importantly, the reactions of various *trans*-β-chlorovinyl compounds result normally in retention of configuration (18, 64, 137, 152–155, 193). The stereochemistry of the virtually unknown *cis*-β-chlorovinyl ketones has not been investigated.

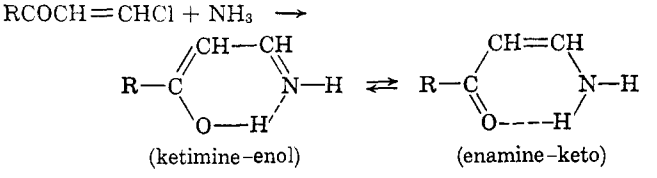
An addition–elimination mechanism has also been considered (66, 216). Again using a primary amine as the nucleophile the following mechanism may be written



This mechanism is unlikely on two counts: (a) many nucleophiles which cannot add to the double bond, such as tertiary amines, readily displace the β-chlorine atom (18), and (b) several studies in deuterated solvents (64) or with tritiated secondary amines (207) on similar systems showed no incorporation of deuterium or tritium into the system.

a. By Ammonia

β-Chlorovinyl ketones react with ammonia to form β-aminovinyl ketones in yields of 78–84% (91, 167) (Table X). The reaction is carried out best by saturation of the solution of the β-chlorovinyl ketone in concentrated ammonium hydroxide with ammonia. The reaction has been described also in the patent literature (151). These β-aminovinyl ketones have also been prepared by the reaction between hydroxymethylene ketones and ammonium salts (15), but the reaction is limited by the poor accessibility of hydroxymethylene ketones. Acetylenic ketones also add ammonia to form β-aminovinyl ketones (23).



It has been shown that β-aminovinyl ketones exist in two separable (38, 91) tautomeric forms (37, 39, 167, 194). For this reason the refractive index of freshly distilled product changes slowly on standing (167). Kochetkov and Dombrovskii (91) came to the conclusion that this change could not be due to a *cis–trans* conversion on the basis of kinetic data ($E_{act} \cong 15.5$ kcal/mole) and in view of the fact that the analogous dialkyl aminovinyl ketones showed no such change. Several other possible structures were also ruled out. Recent work corroborates this view and shows that in nonpolar solvents these compounds exist predominantly in the ketimine–enol form, while in hydroxylic solvents they exist pre-

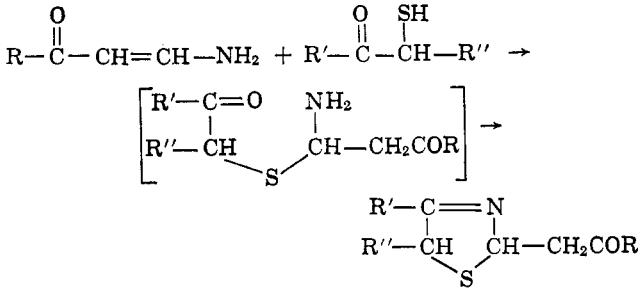
TABLE X

β-AMINOVINYL KETONES: RCOCH=CH—NH_2

R	Bp (mm), °C [Mp, °C] (mixture)	Mp, °C α form	Mp, °C β form	$n^{20}D$ (mixture)	d^{20} (mixture)	% yield	Ref
CH_3	70–71 (3)	...	14–15	1.5668	1.0220	84.4	2, 38, 91, 167
C_2H_5	72–73 (3)	50–51	−32.5 to −31	1.5440	0.9893	77.8	38, 167
n-C_3H_7	84–85 (3)	36–38	−20 to −19	1.5327	0.9650	81.8	38, 167
i-C_3H_7	55–56 (0.5)	69–70	−5.5 to −4.5	1.5273	0.9610	80.2	38, 167
i-C_4H_9	98–99 (2.5)	...	...	1.5221	0.9456	83.5	38, 167
t-C_4H_9	76 (4)	...	32–33.5	1.5119	...	71.6	91
n-C_5H_{11}	103 (2)	...	...	1.5160	0.9342	79.6	167
C_6H_5	[89–90]	...	...	...	...	58–60	2

dominantly in the enamine–keto form (194). Higher temperatures also seem to favor the enol form (91).

These β-aminovinyl ketones are themselves quite reactive and undergo ready condensation with β-chlorovinyl ketones and with a variety of nucleophilic reagents. Thus α-mercapto ketones readily react with β-aminovinyl ketones to form substituted thiazolines in 70–80% yields (2).



Condensation of β-aminovinyl ketones with β-chlorovinyl ketones leads to the formation of 2-alkyl-5-acylpyridines (19, 92). The reaction is carried out by allowing a mixture of β-chlorovinyl ketone and β-aminovinyl ketone (in ratio of 1:2) to stand at room temperature without solvent for several days (see Table XI). The structures of the pyridines were confirmed by oxidation to the known nicotinic acids. A simple displacement of the amino group on the β-chlorine atom did not occur, since this would have led to the formation of 3,4-disubstituted pyridines, and none of these products could be detected (164).

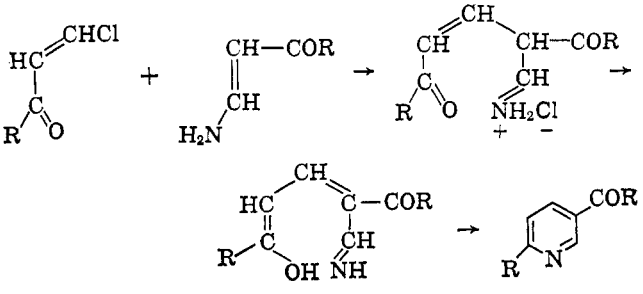
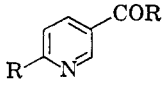


TABLE XI

2-ALKYL-5-ACYLPYRIDINES (92)

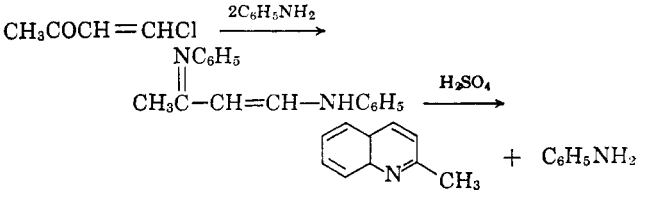


R	Bp (mm), °C	$n^{20}D$	d^{20}_4	% yield
CH_3	95–96 (5)	1.5319	1.0661	50.8
C_2H_5	113–115 (7)	1.5160	1.0200	80
n-C_3H_7	134–135 (8)	1.5117	0.9877	41
n-C_5H_{11}	158–159 (3)	1.5010	0.9464	14

b. Primary Amines

Aliphatic and aromatic primary amines readily replace the β-chlorine atom of β-chlorovinyl ketones (93) (Table XII). The reaction is best run in aqueous solution at 5° using 1.5–2 moles of primary amine to 0.5 mole of β-chlorovinyl ketone. Again these β-aminovinyl ketones may be obtained through the hydroxymethylene ketones (15) or by addition of primary amines to acetylenic ketones (23, 24). If aromatic amines are used in large excess, the initially formed β-aminovinyl ketones will react further to form Schiff bases (58, 66, 68). These Schiff bases have in turn been treated with concentrated sulfuric acid causing ready cyclization to quinolines (66, 68).

$$RCOCH{=}CHCl + R'NH_2 \rightarrow RCOCH{=}CHNHR'$$



When β-chlorovinyl ketones are treated with ethyl β-aminocrotonate (or with ethyl acetoacetate and ammonia), 2,6-dialkyl-3-carbethoxypyridines are formed (94) (see Table XIII). The reaction is similar to the one previously described for the formation of 2-alkyl-5-acylpyridines. Acetylacetone reacts similarly (94).

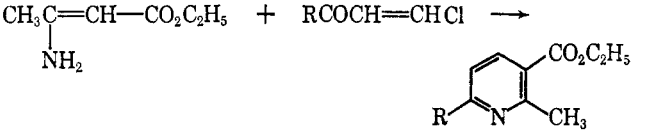


Table XII

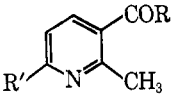
RCOCH=CH—NH—R′

R	R′	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	CH_3	77–78 (13)	1.5687	0.9851	70–90	93
CH_3	C_2H_5	63–64 (4)	1.5427	0.9543	70–90	93
n-C_3H_7	C_2H_5	70 (3)	1.5223	0.9228	70–90	93
n-C_4H_9	CH_3	73–74 (4)	1.5243	0.9292	70–90	93
n-C_4H_9	C_2H_5	76 (4)	1.5140	0.9105	70–90	93
CH_3	$CH_2CH=CH_2$	103–103.5 (17)	...	...	71	7
CH_3	n-C_4H_9	75–80 (18)	...	...	40	60
CH_3	C_6H_5[a]	[103]	...	...	75	58
CH_3	o-$NO_2C_6H_4$[b]	[123–124]	...	...	75	58
CH_3	o-OHC_6H_4[c]	[171–172]	...	...	75	58
CH_3	p-HOC_6H_4	[138–139]	...	...	63	58
CH_3	p-$HO_2CC_6H_4$	[216]	...	...	..	68
C_6H_5	$C_6H_5CH(CH_3)$	180–186 (1) [57–58]	...	...	74	60, 194
C_6H_5	C_6H_5	[140–141]	...	...	..	190
$C_6H_5CH_2$	C_6H_5	[81.5–83]	...	...	..	222
CCl_3	C_6H_5	[108.3–108.6]	...	...	..	199

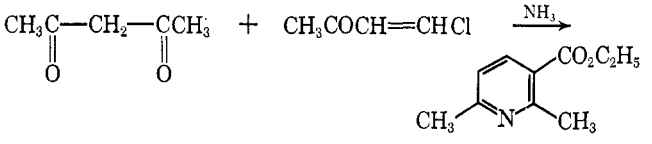
[a] Anil mp 181°. [b] Anil mp 135–136°. [c] Anil mp 163–164°.

Table XIII

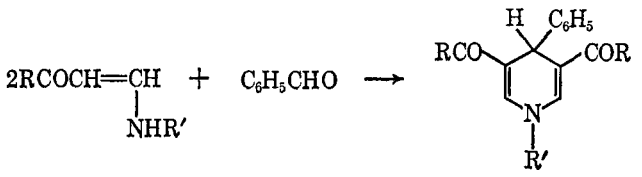
Substituted Pyridines from β-Chlorovinyl Ketones (94)



R	R′	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield
OC_2H_5	CH_3	125–126 (17)	1.5070	1.5065	75
OC_2H_5	n-C_5H_{11}	157–158 (11)	1.4805	0.9960	46
OC_2H_5	n-C_3H_7	138–139 (14)	1.5010	1.069	..
CH_3	CH_3	114–116 (18) [34]	...	...	..



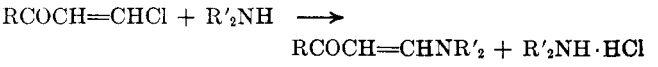
β-Alkylaminovinyl ketones react further with benzaldehyde to form dihydropyridines (59, 60). The reaction is run in ethanol at room temperature with piperidine acetate catalyst; the yields are 30–50%. Starting with the β-chlorovinyl ketones themselves,



the reaction may be conducted without isolation of the intermediate β-aminovinyl ketone.

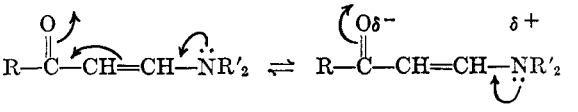
c. By Secondary Amines

Secondary amines react readily with β-chlorovinyl ketones to form the corresponding β-dialkylaminovinyl ketones (Table XIV) in yields of 60–85% (79, 103,



189). The proton magnetic resonance spectrum of 1-dimethylamino-1-buten-3-one prepared in this manner indicates a pure *trans* configuration about the double bond (18). Again, compounds of this type have been prepared from acetylenic ketones (23, 24) and from hydroxymethylene ketones (5, 15). Here the hydrogen bonding (C=O···H–N) observed in the primary amine adducts is absent and thus cannot influence the final configuration of the secondary amine products.

These compounds possess, on the basis of dipole moments (212), high polarization of the type



Consequently, reduced activity at the carbonyl and selective reactions at the double bond are expected chemically and have in fact been observed (80). As shown in Scheme II, hydrogenation of the double bond is preceded by cleavage of the C–N bond. 1-Dimethylamino-1-buten-3-one does not undergo a Diels–Alder condensation with cyclopentadiene even at 180°. On treatment with hydroxylamine, 5-alkylisoxazoles are formed in 65–85% yield; none of the isomeric 3-alkylisoxazoles have been detected. Thus the first step in a fruitful reaction must have been replacement of the β-dialkylamino moiety and not addition to the carbonyl group. This reaction then allows easy preparation of a very difficultly accessible class of compounds. Cleavage of these 5-alkylisoxazoles with sodium ethoxide leads to the formation of β-ketonitriles, again a class of compounds which are very difficult to obtain by other methods. Grignard reagents (36, 80) appear to displace the β-amino moiety, whereas methyl iodide

SCHEME II

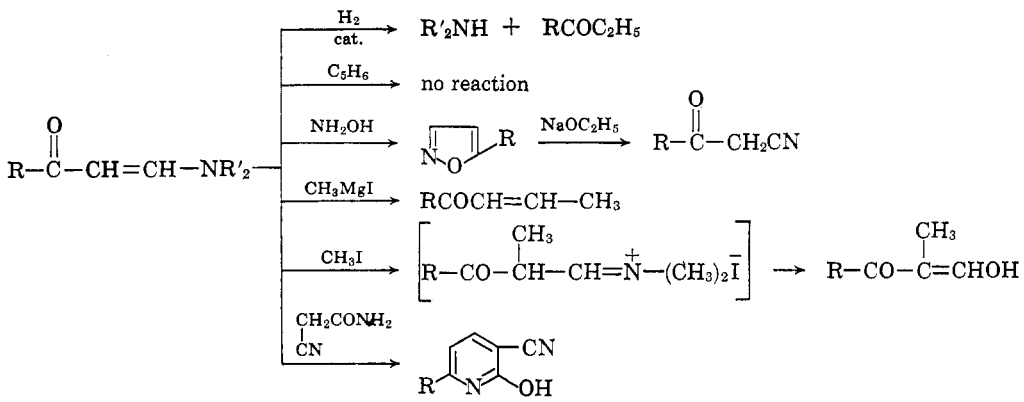


TABLE XIV

β-DIALKYLAMINOVINYL KETONES: RCOCH=CH—NR′₂

R	R′	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	CH_3	101–102 (5)	1.5562	0.9734	76.5	79
CH_3	C_2H_5	124–125 (6)	1.5378	0.9344	83.5	79
CH_3	$(CH_2)_5$	154–155 (7)	1.5730	1.0103	70	79
C_2H_5	CH_3	95–96 (4)	1.5400	0.9533	56.4	103
n-C_3H_7	CH_3	120–121 (5)	1.5364	0.9339	61	79
i-C_3H_7	$-(CH_2)_4-$	105–108 (0.01) [65–66]	...	...	68	189
i-C_3H_7	$(-CH_2CH_2)_2O$	122–124 (0.2)	...	...	63	189
i-C_4H_9	CH_3	124–125 (4)	1.5270	0.9245	66	79
n-C_5H_{11}	CH_3	157–158 (8)	1.5232	0.9213	58	103
C_6H_5	CH_3	[90–91]	...	...	88	103
p-ClC_6H_4	CH_3	[85]	...	...	82.4	103

adds to the α position leading, upon hydrolysis, to the formation of α-methyl hydroxymethylene ketones (80, 103). This reaction is of considerable preparative interest, since the Claisen method often leads to a mixture of isomers. Finally, treatment, with α-cyanoacetamide leads to the formation of 6-alkyl-2-hydroxynicotinonitriles (80). These reactions are summarized in Scheme II.

d. By Tertiary Amines

Tertiary amines readily displace the β-chlorine atom of β-chlorovinyl ketones to form the corresponding quaternary salts (18, 73, 74, 126, 180) in high yields (see Table XV).

$$R—COCH=CHCl + R'_3N \rightarrow RCOCH=CH\overset{+}{N}R'_3\overset{-}{Cl}$$

The reaction is usually run by mixing the reactants in an inert solvent (ether, benzene) at room temperature; the product immediately precipitates from solution. These quaternary salts have also been prepared from the corresponding acetylenic ketones (29).

The quaternary salts are white, slightly hygroscopic solids which, when well purified, may be stored for fairly long periods of time. The proton magnetic resonance spectra show that the quaternary salts formed from these *trans*-β-chlorovinyl ketones lie in the *trans* configuration (18). They readily form sharp melting picrates, and under carefully controlled conditions the corresponding oximes (17).

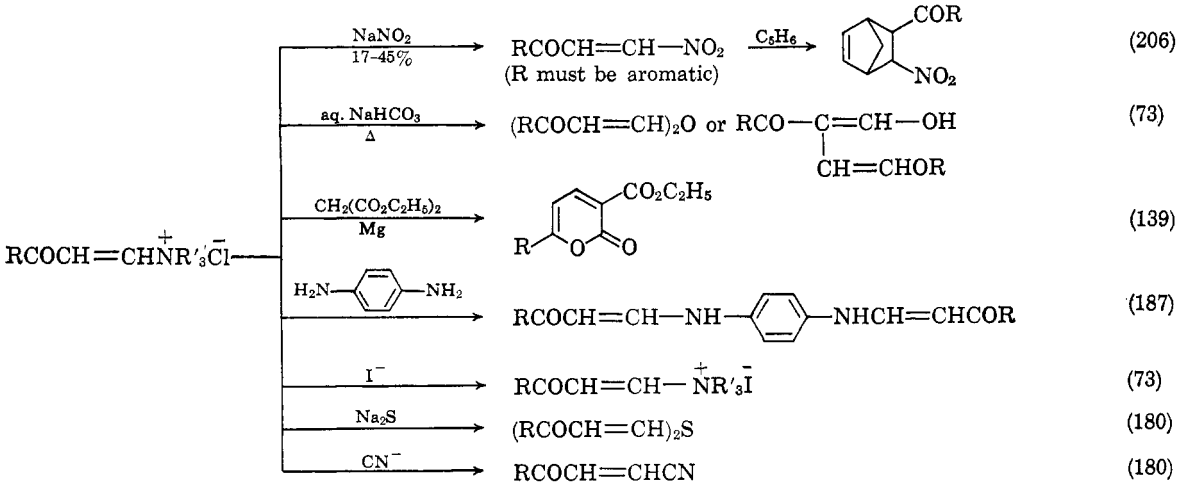
TABLE XV

$RCOCH=CH—\overset{+}{N}R'_3\overset{-}{X}$

R	R′	X⁻	Mp, °C	% yield	Ref
CH_3	CH_3	Cl	154–158 dec	90.5	18, 73, 180
C_2H_5	CH_3	Cl	171–172 dec	88.4	18
n-C_3H_7	CH_3	Cl	142–150 dec	89	18
i-C_3H_7	CH_3	Cl	153–155 dec	82.6	18
i-C_4H_9	CH_3	Cl	108–110 dec	85.8	18
t-C_4H_9	CH_3	Cl	152–154 dec	91.5	18
CH_3	C_2H_5	Cl	160	90	73
n-C_3H_7	C_2H_5	Cl	96–98	89.7	73
C_6H_5	CH_3	Cl	160–161 dec	86.4	18
C_6H_5	C_2H_5	Cl	135–35.5 dec	84	73
o-BrC_6H_4	C_2H_5	Cl	180 dec	71	73
p-NO_2-C_6H_4	C_2H_5	Cl	132 dec	70	73
CH_3	C_2H_5	I	138–140	69.2	73
n-C_3H_7	CH_3	I	147.5–149	87	16
C_4H_3O	C_2H_5	Cl	125–126	...	126
C_4H_3S	C_2H_5	Cl	113–115	...	126
CH_3	C_5H_5	Cl	171–172	92	73, 225
C_2H_5	C_5H_5	Cl	132	...	52

The chemistry of these quaternary salts has been studied quite extensively. The quaternary ammonium moiety appears to be as versatile in its reactions with nucleophiles as the β-chlorine atom of the β-chlorovinyl ketones themselves. Scheme III illustrates the reactions which these quaternary salts have been found to undergo and suggests their use in the synthesis of a wide variety of compounds.

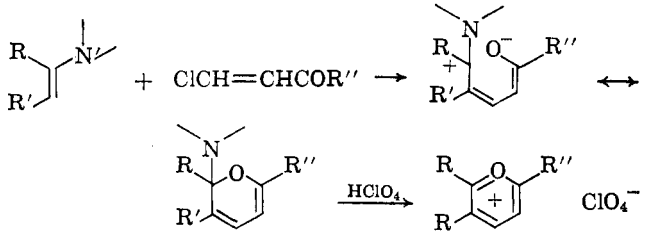
SCHEME III

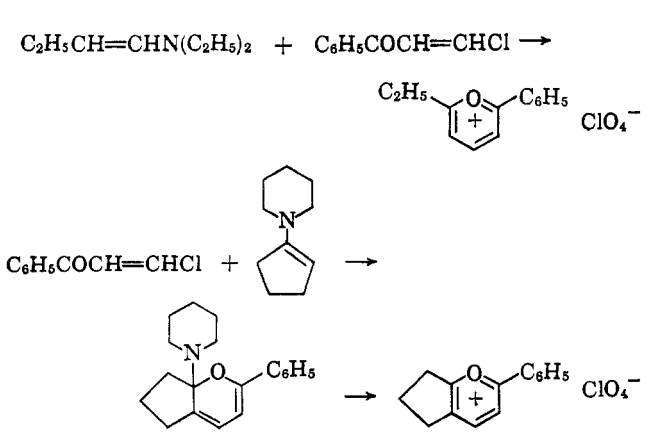


The reactions with nitrite ion and cyanide ion are of special interest, since neither ion readily replaces the β-chlorine atom of β-chlorovinyl ketones. The β-cyanovinyl ketones have in turn been studied extensively, and it has been found that the carbonyl group polarizes the double bond more extensively than does the cyanide group. The reactions which have been investigated using these β-cyanovinyl ketones are summarized in Scheme IV.

e. By Enamines

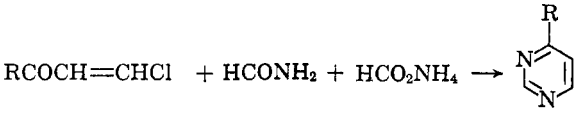
β-Chlorovinyl ketones react readily with enamines to form colored, occasionally crystalline adducts in 70–75% yields which on treatment with perchloric acid are converted into pyrylium perchlorates in 50–60% yields (210). Enamines of aldehydes react to form 2,5-disubstituted pyrylium salts, whereas enamino ketones lead to the formation of bicyclic pyrylium salts (see Table XVI).





f. By Formamide, Amidines, and Alkylguanidines

It has been found that formamide readily condenses with β-chlorovinyl ketones to form 4-alkylpyrimidines (25, 218) (see Table XVII).



In a similar reaction, Price and Zomlefer (197) attempted unsuccessfully to condense methyl β-chlorovinyl ketone with amidines.

In addition, the condensation of β-chlorovinyl ketones with alkylguanidines to form 2-alkylamino-4-alkylpyrimidines has been reported (218).

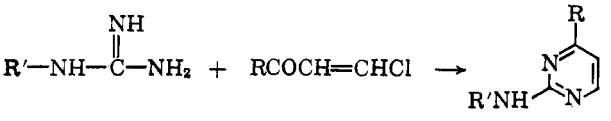
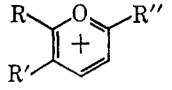


TABLE XVI

PYRYLIUM SALTS FROM β-CHLOROVINYL KETONES (210)



R	R'	R''	Mp, °C
C_2H_5	H	C_6H_5	152–153
	$-(CH_2)_3-$	C_6H_5	161–162
	$-(CH_2)_4-$	C_6H_5	177–178
	$-(CH_2)_5-$	C_6H_5	146–147
		C_6H_5	215
		C_6H_5	215–216

SCHEME IV

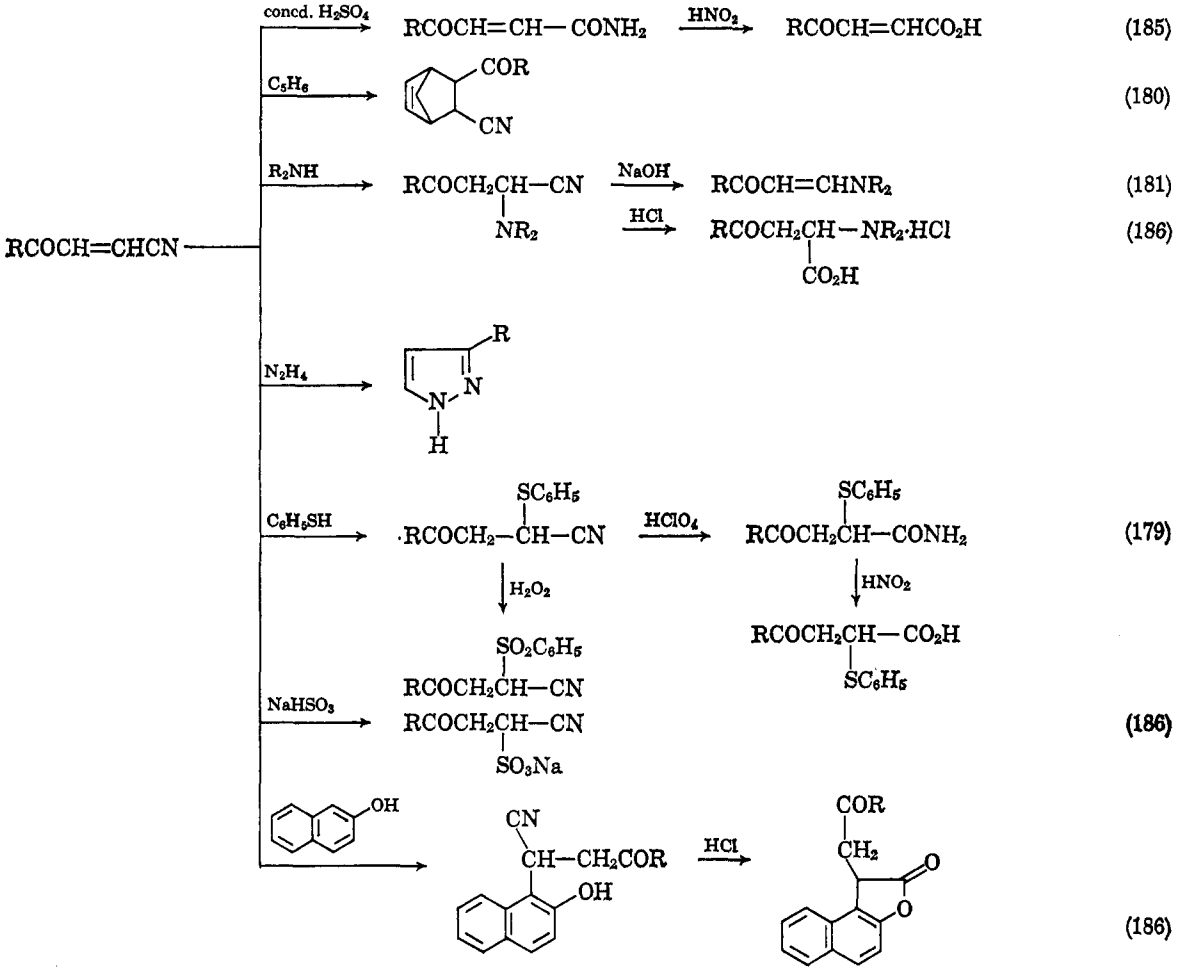
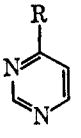


TABLE XVII

4-ALKYLPYRIMIDINES (25, 218)



R	Bp (mm), °C	$n^{20}D$	% yield
CH_3	138–142 (760)	1.4942	40
C_2H_5	158–159 (760)	1.4928	55
n-C_3H_7	94–95 (50)	1.4883	60
i-C_4H_9	116–117 (86)	1.4820	60

g. By Aliphatic and Aromatic Alcohols

Treatment of β-chlorovinyl ketones with aliphatic alcohols leads to the formation of β-ketoacetals through the addition of 2 moles of alcohol (Table XVIII) (171, 223). The reaction proceeds apparently by the initial formation of vinyl ethers which have been isolated in only

$$RCOCH{=}CHCl + R'OH \longrightarrow$$

$$RCOCH{=}CHOR' \xrightarrow{R'OH} RCOCH_2CH(OR')_2$$

two instances. Thus treatment of phenyl β-chlorovinyl ketone with sodium hydroxide dissolved in cold, absolute ethanol led to an 85% yield of the simple displacement product (131).

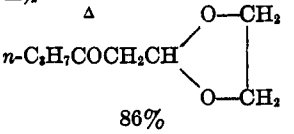
$$C_6H_5COCH{=}CHCl + CH_3OH \xrightarrow{NaOH} \underset{85\%}{C_6H_5COCH{=}CH{-}OCH_3}$$

The use of sodium methoxide and methanol at room temperature resulted in addition to 2 moles of methanol. Alternatively, treatment of these β-ketoacetals with p-toluenesulfonic acid (TsOH) in acetic anhydride has been reported to yield the vinyl ethers (52).

$$C_2H_5COCH_2CH(OCH_3)_2 \xrightarrow{TsOH} C_2H_5COCH{=}CH{-}OCH_3$$

Ethylene glycol, as expected, forms the more stable dioxolane derivatives (104, 125). Alternatively, simply heating the above β-ketoacetals with ethylene glycol also leads to the formation of these dioxolanes (125).

$$n\text{-}C_3H_7COCH_2CH(OCH_3)_2 + (CH_2OH)_2 \xrightarrow[\Delta]{KOH}$$



86%

TABLE XVIII

β-KETOACETALS: $RCOCH_2CH(OR')_2$

R	R'	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	CH_3	69 (20)	1.4231	0.9978	70	160, 161, 171, 196
CH_3	C_2H_5	76–77 (10)	1.4226	0.9440	50	171
CH_3	nC_4H_9	114–114.5 (20)	1.4320	0.9131	60	160, 161, 171
CH_3	C_6H_5	168–169 (1) [31–32]	...	...	26	171
C_2H_5	CH_3	80 (12)	1.4278	...	...	52
C_2H_5	C_2H_5	86.5–87 (10)	1.4240	0.9380	50	171
n-C_3H_7	C_2H_5	84–85 (5)	1.4347	0.9228	47	171
i-C_3H_7	C_2H_5	86–87 (11)	1.4225	0.9229	42.3	78
i-C_4H_9	CH_3	81 (7)	1.4204	0.939	90	196
i-C_4H_9	C_2H_5	112 (18)	...	...	...	160, 161
n-C_5H_{11}	C_2H_5	129–130 (19)	1.4334	0.9117	51.8	96
i-C_5H_{11}	CH_3	124 (25)	1.4260	0.932	80	196
i-C_6H_{13}	CH_3	97 (3)	1.4300	0.925	84	196
n-C_7H_{15}	CH_3	110–112 (4.5)	1.4372	0.9245	...	221
n-$C_{15}H_{31}$	CH_3	[25.2–25.7]	...	...	...	221
CH_3	CH_2	82–83 (9)	1.4400	1.084	51	125
C_2H_5	CH_2	90–91 (10)	1.4420	1.0741	51	125
n-C_3H_7	CH_2	92–93 (7)	1.4427	1.0440	56	125
i-C_4H_9	CH_2	92–92 (4.5)	1.4429	1.0181	60	125
n-C_5H_{11}	CH_2	112–113 (16)	1.4471	1.0062	65	125
C_6H_5	CH_2	[58.5–59]	...	...	85	125
p-$CH_3C_6H_4$	CH_2	[47.5–48]	...	...	62	131
m-$CH_3C_6H_4$	CH_2	[48–49]	...	...	75	131
o-$CH_3C_6H_4$	CH_2	[36–37]	...	...	79	131
o-ClC_6H_4	CH_2	137–138 (2) [16–18]	1.5852	1.2744	46	131
p-ClC_6H_4	CH_2	[45–46]	...	...	74	131
p-BrC_6H_4	CH_2	[55–56]	...	...	82	131
p-$CH_3OC_6H_4$	CH_2	[66.5–67.5]	...	...	74	131

These β-ketoacetals are of great interest, because they react in the same manner as the much more difficultly accessible β-ketoaldehydes, but are more stable and easier to handle (124). A recent review article is devoted to the reactions and properties of these β-ketoacetals and indicates the importance of these compounds in organic synthesis (122).

Phenols react with β-chlorovinyl ketones in the presence of base to form the expected aryl ketovinyl ethers (Table XIX).

$$RCOCH{=}CHCl + ArOH \rightarrow RCOCH{=}CH{-}OAr$$

In the case of the reaction between methyl β-chlorovinyl ketone and phenol in the presence of sodium, products resulting from the addition of 1 and 2 moles of phenol were isolated (171).

$$CH_3COCH{=}CHCl + C_6H_5OH \xrightarrow{Na} \underset{31\%}{CH_3COCH{=}CHOC_6H_5} + \underset{26\%}{CH_3COCH_2CH(OC_6H_5)_2}$$

Interestingly, methyl β-phenoxyvinyl ketone in the presence of sodium ethoxide is converted into the diethyl acetal of acetylacetaldehyde (132).

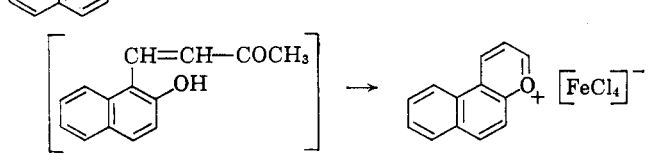
$$CH_3COCH{=}CH{-}OC_6H_5 + C_2H_5OH \xrightarrow{NaOC_2H_5} \underset{20\%}{CH_3COCH_2CH(OC_2H_5)_2}$$

TABLE XIX

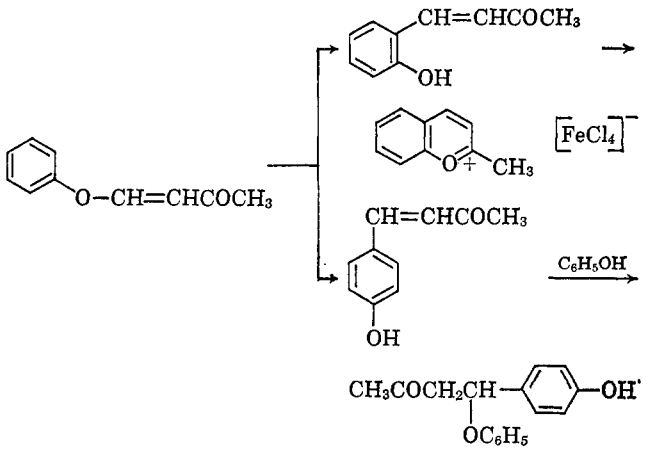
β-ARYLOXYVINYL KETONES: RCOCH=CH—O—Ar

R	Ar	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	C_6H_5	113–114 (2)	1.5610	1.0771	80–87	132, 176
CH_3	p-$CH_3C_6H_4$	137–138 (8)	1.5535	1.0540	80–87	132
CH_3	o-$NO_2C_6H_4$	[53]	...	...	57	218
CH_3	1-$C_{10}H_7$	195–196 (7)	...	...	80–87	132
CH_3	2-$C_{10}H_7$	[60]	...	...	63	132
n-C_3H_7	C_6H_5	124–125 (4)	1.5421	1.0348	80–87	132
i-C_4H_9	C_6H_5	141–142 (4)	1.5340	1.0134	80–87	132

In acetic acid and in the presence of ferric chloride, phenols react with β-chlorovinyl ketones to form in high yields the intensely colored benzopyrylium, naphthopyrylium, and flavylium salts (Table XX). The formation of these colored salts may be used as qualitative tests for the presence of β-chlorovinyl ketones and for derivatives in their characterization. These salts form *via* an initial Fries rearrangement followed by cyclization (174).

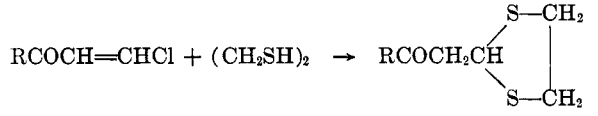


If the *para* position is not blocked, the yields are low (10–15%) due to preferential rearrangement to the *para* position.



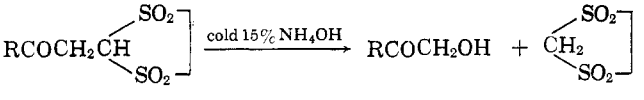
h. By Thiols

Aliphatic thiols react in precisely the same manner as the aliphatic alcohols forming β-thioacetals (Table XXI). Moreover, 1,2-ethanedithiol readily forms the corresponding dithiolane adducts, 50–90% yields (123).

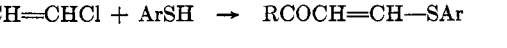


No thioethers have been isolated from these reactions. Thus if one wishes to prepare compounds of the type RCOCH=CHSR′ where R is aliphatic, one must start with the corresponding acetylenic ketones (23).

These β-ketothioacetals, in contrast to the corresponding acetals, are quite stable in acid media and are of interest because they enter into reactions typical of the little known but highly reactive β-ketoaldehydes. As expected these β-ketothioacetals are readily hydrogenated to the corresponding ethyl ketones. They form pyrylium salts on treatment with ferric chloride in acetic acid, and are oxidized by hydrogen peroxide to the corresponding disulfones. The disulfones are useful in synthesis, because they are very easily hydrolyzed to α-hydroxy ketones (123).



Treatment of β-chlorovinyl ketones with thiophenols in aqueous alkaline media results in the formation of the corresponding vinyl thioethers in high yields (Table XXII).

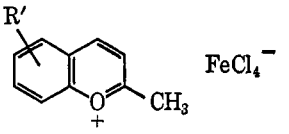


These are colorless, stable solids which, in contrast to the corresponding β-aryloxyvinyl ketones, do not undergo a Diels–Alder condensation with cyclopentadiene (133). They form 2,4-dinitrophenylhydrazones which have not been reported to cyclize to pyrazoles. However, hydroxylamine addition leads to approximately equal amounts of both the 3- and 5-alkylisoxazoles.

The thiophenoxy group is easily hydrolyzed in acidic or basic solution and may be oxidized to either the sulfoxide or the sulfone under the proper conditions (134). The identical sulfones are produced by the addition of sodium phenylsulfinate to β-chlorovinyl ketones (102). The sulfones and the phenylhydrazones of the sulfones reveal an intense band at 983 cm^{-1} in the infrared indicating a *trans* configuration about the double bond. On irradiation with ultraviolet light, the *trans*-sulfone was converted into the *cis* isomer, which exhibited no

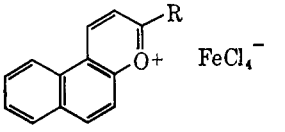
TABLE XX

a. BENZOPYRYLIUM SALTS



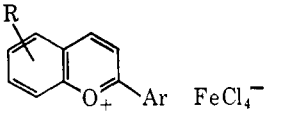
Phenol used	R′	Mp, °C	% yield	Ref
C_6H_5OH	H	125–125.5	15	172
p-$CH_3C_6H_4OH$	6-CH_3	103–105	53	172
p-HOC_6H_4OH	6-OH	122–123	46	172
m-HOC_6H_4OH	7-OH	145	59	172
2,4,6-$(OH)_3C_6H_3$	5,7-$(OH)_2$	7300	..	171

b. NAPHTHOPYRYLIUM SALTS



R	Mp, °C	% yield	Ref
CH_3	151–152	74	173
n-C_3H_7	124	93	173
i-C_3H_7	100.5 (157)	71.4	173
i-C_4H_9	103	73	173
t-C_4H_9	195–197.5	56	87
n-C_5H_{11}	74	50	173
$CH_3CH{=}CH$	153–157 dec	67	111
$(CH_3)_2C{=}CH$	186–188 dec	71.5	111
C_6H_5	187.5–188	90	172
p-$CH_3C_6H_4$	166–168	80	172
p-$CH_3OC_6H_4$	216–217	62	172
C_7H_8	105–107		95
C_4H_3S	176–177	66	126

c. FLAVYLIUM SALTS



Ar	Phenol used	R	Mp, °C	% yield	Ref
C_6H_5	C_6H_5OH	H	137–138	10	172
C_6H_5	p-$CH_3C_6H_4OH$	6-CH_3	170–171.5	60	172
p-$CH_3C_6H_4$	p-$CH_3C_6H_4OH$	6-CH_3	199–200	89	172
p-BrC_6H_4	p-$CH_3C_6H_4OH$	6-CH_3	183	34	172
C_6H_5	p-HOC_6H_4OH	6-OH	158–159	60	172
C_6H_5	m-HOC_6H_4OH	7-OH	163–164	87	172
p-BrC_6H_4	p-HOC_6H_4OH	6-OH	191–191.5	47	172
p-BrC_6H_4	m-HOC_6H_4OH	7-OH	169	86	172
p-$CH_3OC_6H_4$	m-HOC_6H_4OH	7-OH	176–177	81	172
C_6H_5	2,4,6-$(HO)_3C_6H_2$	5,7-$(OH)_2$	>250	78	172

TABLE XXI (123)

β-KETOTHIOACETALS: $RCOCH_2CH(SR')_2$

R	R'	Bp (mm),°C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Sulfone Mp, °C	Sulfone % yield
C_6H_5	C_2H_5	[44–45]	...	...	68		
CH_3	—CH_2—	143–145 (10)	1.5579	1.2080	60	124.5–125	97
C_2H_5	—CH_2—	130–132 (8)	1.5464	1.1693	51	149.5–150	92
n-C_3H_7	—CH_2—	136–138 (5)	1.5381	1.1311	49	128.5–129	90
C_6H_5	—CH_2—	[74–75]	...	...	50		
p-BrC_6H_4	—CH_2—	[101–102]	...	...	90		
m-$CH_3C_6H_4$	—CH_2—	[66–66.5]	...	...	50		

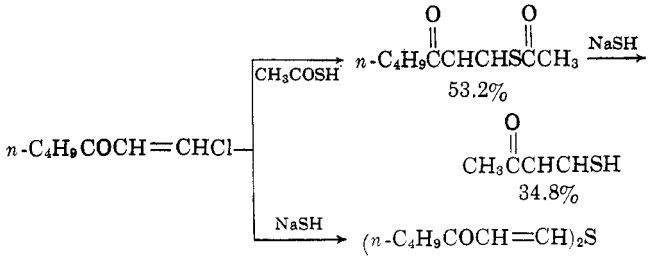
TABLE XXII (133, 134)

β-THIOPHENOXYVINYL KETONES: RCOCH=CH—SAr

R	Ar	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Sulfoxide Mp, °C	Sulfoxide % yield	Sulfone Mp, °C	Sulfone % yield
CH_3	C_6H_5	126–129 (2) [30]			55	65-66	59.6	61.2	30
CH_3	o-$NO_2C_6H_4$	[85–86]			43				
CH_3	p-$CH_3C_6H_4$	[60.5–61.5]	1.5922	1.0740	100				
n-C_3H_7	C_6H_5	126–128 (1)	1.5837	1.0610	86			64-65	43
i-C_4H_9	C_6H_5	149–151 (4)	1.5759	1.0310	83	96–97	23.3	82–84	46
i-C_4H_9	p-$CH_3C_6H_4$	154–156 (2)			60			86–87	49
C_6H_5	C_6H_5	[79.5–80.5]			100	126–127.5	60.7	112–112.5	~96
C_6H_5	p-$NO_2C_6H_4$	[138-138.5]			100				
C_6H_5	p-$CH_3C_6H_4$	[85.5 86.5]			100				

absorption in the 990–965-cm^{-1} region. The ultraviolet spectra corroborate the assignment of *cis* and *trans* to these isomers.

Finally, thioacetic acid as well as sodium hydrosulfide have been found to react readily with β-chlorovinyl ketones in the presence of base (208).

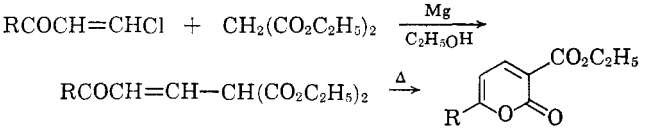


i. By Organic Anions

There are a large number of reactions in which an active hydrogen atom is replaced by a ketovinyl group (83, 118). These reactions are summarized in Table XXIII. The reaction works well with compounds containing only one active hydrogen atom, such as alkylacetoacetates (100), alkylmalonates (113), α-alkylbenzoylacetates (12, 13), β-diketones containing only one active hydrogen atom (98), esters of cyclic β-ketoacids (101), nitrocyclohexane (88, 90), etc. However, ketovinylation of α-acetylacetoacetate was unsuccessful. As an example of the utility of these reactions in synthesis (96, 97, 117), Scheme V is given (p 180).

When more than one active hydrogen atom is present, the reaction does occur, but the ketovinylation product quickly reacts further so that isolation of the intermediate is very difficult. For instance, in the case of ethyl acetoacetate, treatment, with β-chlorovinyl ketones leads to the formation of two products, the percentage of each being dependent upon the relative proportions of starting materials used (119, 120). If an excess of ethyl acetoacetate is used, the major product (40%) is a phenol. With excess β-chlorovinyl ketone, however, the major product (80%), resulting from a Diels–Alder addition to the ketovinylation product, is a diacylbenzoic acid (Scheme VI).

Under special conditions it is feasible to ketovinylate ethyl malonate. Treating the ethoxymagnesium derivative of ethyl malonate with β-chlorovinyl ketones leads to the formation in high yields of esters of β-ketovinylmalonic esters (114, 116). Ketovinylation of ethyl acetoacetate under these conditions failed.



The configuration of these ketovinylation products has been shown to be *trans*, the infrared spectra showing a strong band in the 986–984-cm^{-1} region (102). Thus displacement of the β-chlorine atom has again occurred without change in configuration.

j. By Inorganic Anions

A series of inorganic anions have been used successfully to replace the β-chlorine of β-chlorovinyl ketones (see Table XXIV). Thus treatment of β-chlorovinyl

ketones with sodium iodide in boiling acetone yields the corresponding β-iodovinyl ketones (77), which recently have been shown by proton magnetic resonance to have a *trans* configuration about the double bond (18).

Use of potassium thiocyanate in water results in the formation of β-thiocyanovinyl ketones (77). These compounds on treatment with aniline form the corresponding anils, while addition of methanol results in the formation of β-ketoacetals arising from displacement of the thiocyano moiety and addition of methanol to the double bond.

Recently β-chlorovinyl ketones have been found to react with sodium azide to form the corresponding β-azidovinyl ketones (182). However, due to difficulties

TABLE XXIII

KETOVINYLATION PRODUCTS

a. $RCOCH{=}CHCl + R'CO{-}CR''H{-}CO_2C_2H_5 \rightarrow RCOCH{=}CH{-}\underset{\displaystyle COR'}{\underset{|}{C}}R''{-}CO_2C_2H_5$

R	R′	R″	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	CH_3	C_2H_5	108–110 (1)	1.4670	1.0550	64.5	100
C_2H_5	CH_3	C_2H_5	115–117 (1)	1.4665	1.0415	52	100
n-C_3H_7	CH_3	C_2H_5	120–122 (1)	1.4657	1.0270	72	100
CH_3	CH_3	n-C_4H_9	139–140 (2)	1.4662	1.0274	55	100
C_2H_5	CH_3	n-C_4H_9	129–131 (2)	1.4660	1.0157	54	118
n-C_3H_7	CH_3	n-C_4H_9	137–138 (1)	1.4650	1.0007	75	100
C_2H_5	n-C_3H_7	C_2H_5	125–126 (1)	1.4640	1.0070	45	12
n-C_3H_7	n-C_3H_7	C_2H_5	129–130 (0.8)	1.4650	0.9982	53.5	12
C_6H_5	n-C_3H_7	C_2H_5	166–167 (1)	1.5214	1.0702	53	12
C_6H_5	C_6H_5	C_2H_5	[96]	...	...	74	12
p-BrC_6H_4	C_6H_5	C_2H_5	[80]	...	...	22	12
CH_3	C_6H_5	CH_3	141–143 (0.3)	1.5257	1.1102	59	13
C_2H_5	C_6H_5	CH_3	129–131 (0.03)	1.5225	1.0944	57.3	13
n-C_3H_7	C_6H_5	CH_3	133–135 (0.03) [54]	...	1.5190	...	13
i-C_3H_7	C_6H_5	CH_3	135–138 (0.06)	1.5162	1.0711	42.1	13
i-C_4H_9	C_6H_5	CH_3	145–148 (0.06) [18]	1.5148	1.0621	41.5	13
n-C_5H_{11}	C_6H_5	CH_3	162–165 (0.1) [38.5]	...	...	56.3	13
C_6H_5	C_6H_5	CH_3	[63–63.5]	...	...	50.3	13
CH_3	C_6H_5	C_2H_5	137–139 (0.06)	1.5270	1.0983	47.4	13
CH_3	$-(CH_2)_3-$		147–149 (3)	1.4880	1.1112	65	101
C_2H_5	$-(CH_2)_3-$		153–155 (3)	1.4862	1.0958	64	101
n-C_3H_7	$-(CH_2)_3-$		149–152 (2)	1.4840	1.0767	67	101
C_6H_5	$-(CH_2)_3-$		154–156 (0.03) [60–65]	...	...	49	101
CH_3	$-(CH_2)_4-$		163–164 (4) [28.5–29]	...	...	64	101
n-C_3H_7	$-(CH_2)_4-$		168–169 (2)	1.4668	...	61	101
C_6H_5	$-(CH_2)_4-$		[72–73]	...	...	65	101
CH_3	C_2H_5O	C_2H_5	125–126 (2)	1.4543	1.0598	55.6	113
CH_3	C_2H_5O	n-C_3H_7	163 (8)	1.4553	1.0437	56.3	113
CH_3	C_2H_5O	n-C_4H_9	154–156 (4)	1.4559	1.0326	35.2	113
C_2H_5	C_2H_5O	n-C_3H_7	169–171 (9)	1.4575	1.0350	94	113
C_7H_{15}	C_2H_5O	n-C_3H_7	177–178 (1)	1.4581	0.9901	70	113
C_6H_5	C_2H_5O	n-C_3H_7	204–205 (4) [39]	1.5112	1.1007	63.7	113

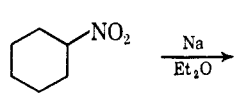
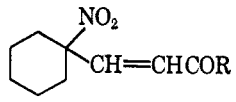
b. $RCOCH{=}CH{-}Cl + R'{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}\underset{|}{CH}{-}\overset{\displaystyle O}{\overset{\|}{C}}{-}R'' \rightarrow RCO{-}CH{=}CH{-}\underset{\displaystyle COR''}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}COR'$

R	R′	R″	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	CH_3	CH_3	100–101 (1)	1.4860	1.0609	59	98
C_2H_5	CH_3	CH_3	106–107 (1)	1.4822	1.0400	44	98
n-C_3H_7	CH_3	CH_3	116–118 (1)	1.4795	1.0215	59	98
CH_3	$-(CH_2)_3-$		[61–63.5]	...	...	26	98
CH_3	$-CH_2C(CH_3)_2CH_2-$		147–149 (2) [37–38]	...	...	35	98

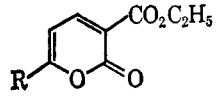
c. $RCOCH{=}CHCl + CH_2(CO_2C_2H_5)_2 \xrightarrow{Mg,C_2H_5OH} RCOCH{=}CH{-}CH(CO_2C_2H_5)_2$

R	Bp (mm), °C	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	121–122 (3)	1.1086	1.1086	69.6	114
C_2H_5	130–134 (2)	1.4611	1.0856	44	114
n-C_3H_7	90–93 (0.06)	1.4581	1.0494	63	114

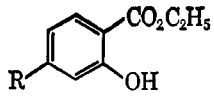
TABLE XXIII (*Continued*)

d. RCOCH=CH—Cl +  $\xrightarrow[Et_2O]{Na}$ 

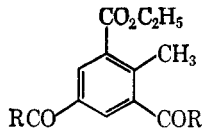
R	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	110–112 (0.4)	1.5018	1.1079	34	90
C_2H_5	118–120 (0.4)	1.5000	1.0871	34	90
n-C_3H_7	118–120 (0.1)	1.5008	1.0700	33	90
C_6H_5	[124–124.5]	...	...	23	90
p-$CH_3C_6H_4$	[95–96]	...	...	22	90
p-BrC_6H_4	[175–176]	...	...	14	90
p-ClC_6H_4	[113–113.5]	...	...	32	90

e. RCOCH=CH—Cl + $CH_2(CO_2C_2H_5)_2$ $\xrightarrow{Mg}$ $\xrightarrow{\Delta}$ 

R	Bp (mm), °C [mp, °C]	$n^{20}D$	n^{20}_4	% yield	Ref
CH_3	[86]	...	...	53	114
C_2H_5	162–163 (7)	1.5265	1.1767	92	115
n-C_3H_7	145–148 (1)	1.5170	1.1285	43	114, 115
n-C_5H_{11}	147–150 (0.5)	1.5128	1.0994	44	115
n-C_7H_{15}	161–162 (0.5)	1.5079	1.0555	38.3	115
C_6H_5	[105]	...	...	55	114, 115

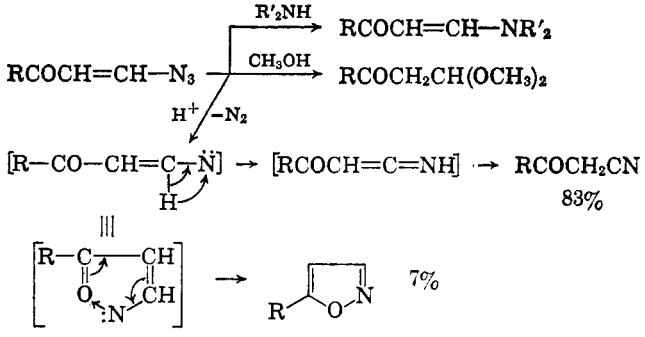
f. RCOCH=CHCl + $CH_3CO—CH_2CO_2C_2H_5$ $\longrightarrow$ 

R	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	129–132 (11)	1.5174	1.0915	39.2	119
C_2H_5	141–142 (15)	1.5162	1.0784	18	119
n-C_3H_7	138–140 (6)	1.5165	1.0836	17	119
i-C_4H_9	148.5–150 (9)	1.5118	1.0878	18	119

g. RCOCH=CHCl + $CH_3COCH_2CO_2C_2H_5$ $\longrightarrow$ 

R	Bp (mm), °C [mp, °C]	$n^{20}D$	d^{20}_4	% yield	Ref
CH_3	160—165 (1) [61]	...	...	81	120
C_6H_5	[104]	...	...	85	120
p-ClC_6H_4	[110]	...	...	58	120

in isolation and purification of the azidovinyl ketones prepared by this method, the preferred synthesis of these compounds involves treatment of the corresponding trimethylamine quaternary salts with sodium azide. The β-azidovinyl ketones are quite unstable; for instance, methyl β-azidovinyl ketone, which was prepared from the quaternary salt, exploded violently on heating. However, the azide moiety is mobile and is readily displaced by other nucleophiles as is illustrated in the following diagram. In addition, as is usually the case with azides, the β-azidovinyl ketones are unstable in the presence of acids and rearrange with elimination of nitrogen, probably *via* an azine intermediate.



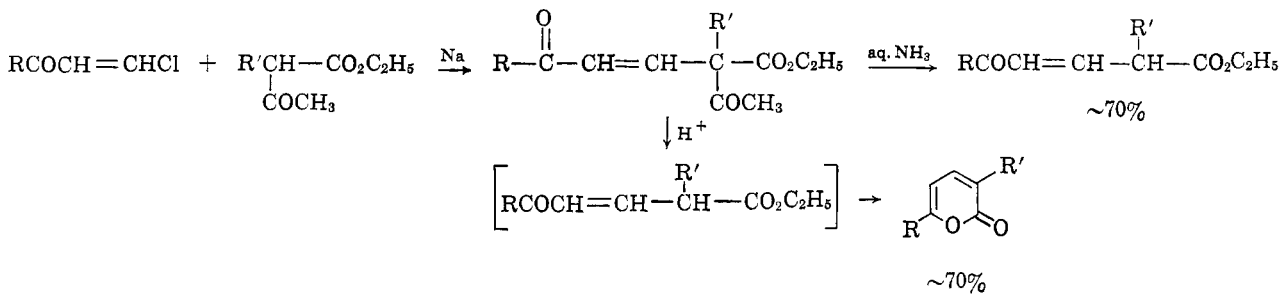
k. By Dimethylcadmium

β-Chlorovinyl ketones might be considered in one sense to be vinylogous acid chlorides. This point of view has been suggested by the reaction between β-chlorovinyl ketones and dialkylcadmium reagents, which resulted in replacement of the β-chlorine by an alkyl group (148) (see Table XXV).

$$2RCOCH=CHCl + R'_2Cd \rightarrow 2RCOCH=CHR' + CdCl_2$$

In one instance both *cis* and *trans* products were isolated.

SCHEME V



SCHEME VI

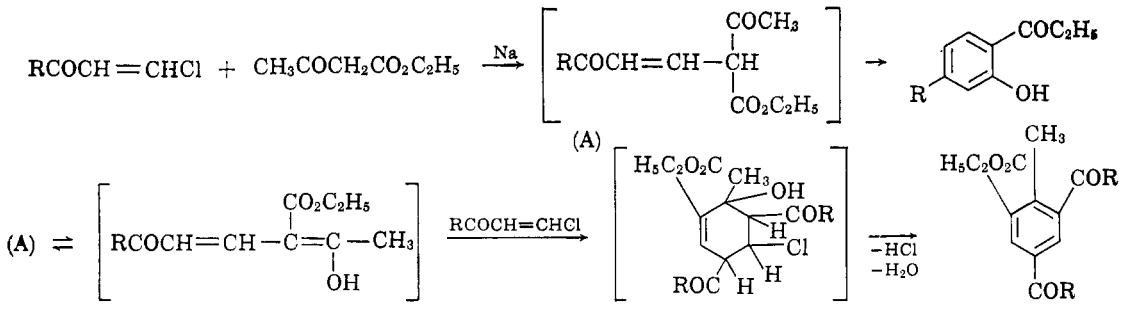


TABLE XXIV

RCOCH=CH—X

R	X	Bp (mm), °C [mp, °C]	$n^{20}D$	% yield	Ref
CH_3	I	[55–56]	...	74.8	77
n-C_3H_7	I	107–109 (25) [28–29]	...	55.5	77
i-C_4H_9	I	92–94 (5)	1.5320	51.8	77
CH_3	SCN	[39–40]	...	73	77
n-C_3H_7	SCN	129–130 (8) [31–32]	...	77	77
i-C_4H_9	SCN	125–126 (6)	1.5195	65	77
C_6H_5	SCN	[94]	...	85	190
CH_3	N_3	...	1.5442	54	182
C_6H_5	N_3	[85–86]	...	90	182
o-ClC_6H_4	N_3	[86–87]	...	88	182
p-ClC_6H_4	N_3	[68–70]	...	94	182
p-BrC_6H_4	N_3	[96–97]	...	97	182

1. By Aromatic Ring Systems (Friedel–Crafts Condensations)

β-Chlorovinyl ketones react with olefins at −10° in the presence of stannic chloride to form α,β-unsaturated ketones (89, 148) (Table XXVIa). Even acetylene reacts with β-chlorovinyl ketones in the presence of stannic chloride (89, 148) (Table XXVIb).

Phenyl ethers readily undergo Friedel–Crafts condensations with β-chlorovinyl ketones (Table XXVIc).

$$RCOCH{=}CHCl + ArOR' \rightarrow RCOCH{=}CH{-}C_6H_4{-}OR'$$

The reaction is carried out best by adding an equimolar amount of stannic chloride in carbon tetrachloride to a chilled solution of the β-chlorovinyl ketone and phenyl ether (14). In this way yields of β-arylvinyl ketones are usually 50–70%. Condensation occurs *para* unless the *para* position is blocked, in which case *ortho* substitution occurs.

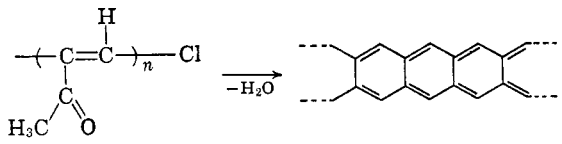
It has been found that the condensation of β-chlorovinyl ketones even with active benzene homologs does not occur under the above conditions. However, the condensation of benzene and its homologs can be effected readily in the presence of aluminum chloride and a strong current of moist hydrogen chloride (184).

$$RCOCH{=}CHCl + ArH \rightarrow RCOCH{=}CH{-}Ar + HCl$$

Almost no reaction occurs under anhydrous conditions; under these conditions methyl as well as phenyl β-chlorovinyl ketone react readily with mesitylene and *m*-xylene, but not with benzene or toluene. On the other hand, chloromethyl β-chlorovinyl ketone reacts not only with *m*- and *p*-xylenes, but with toluene and benzene also.

4. *Miscellaneous Studies*

The use of β-chlorovinyl ketones in the formation of various types of polymers has been studied (178, 187). The electrical and magnetic properties of these polymers have been investigated. In addition, β-chlorovinyl ketone polymers act as catalysts in the oxidation and dehydrogenation of alcohols. One structure which has been proposed for the polymer from methyl β-chlorovinyl ketone is



The polymer was observed to lose water on prolonged heating.

Table XXV (148)

RCOCH=CH—R′

R	R′	Bp (mm), °C	n_D (t, °C)	d_4 (t, °C)	% yield
CH_3	CH_3	121 (760)	1.4363 (19.8)	0.859 (19.8)	18
CH_3	n-C_3H_7	63 (19)	1.4452 (18.6)	0.860 (18.6)	39
CH_3	n-C_4H_9	72 (23)	1.4486 (19.2)	0.864 (19.2)	48
CH_3	n-C_5H_{11}	85 (12)	1.4501 (21)	0.857 (12)	48
CH_3	i-C_5H_{11}	86 (17)	1.4479 (19.5)	0.847 (19.5)	50
CH_3	n-C_6H_{13} (*cis*)	95 (15)	1.4429 (19.1)	0.836 (19.1)	54
	(*trans*)	104 (13)	1.4506 (19)	0.848 (19.0)	54
CH_3	C_6H_5	88 (0.5)	1.5967 (19.3)	1.042 (19.3)	34
CH_3	—CH=CH−CH_3	70 (13)	1.5208 (20.6)	0.891 (20.6)	18
n-C_3H_7	CH_3	59 (15)	1.4468 (20)	0.844 (20)	32
n-C_3H_7	n-C_5H_{11}	85 (1)	1.4522 (21.3)	0.850 (21.3)	61
n-C_3H_7	C_6H_{11}	101 (1)	1.4808 (22.1)	0.909 (22.1)	60
n-C_3H_7	—CH=CH—CH_3	71 (1)	1.5062 (22.9)	0.885 (22.9)	30
n-C_3H_7	—CH=$C(CH_3)_2$	88 (0.6)	1.5150 (22.2)	0.889 (22.2)	35
n-C_3H_7	—$C(CH_3)$=$C(CH_3)_2$	94 (0.5)	1.5145 (21.6)	0.897 (21.6)	33

Table XXVI

Friedel-Crafts Condensation Products (148)

a. RCOCH=CH—R′

R	R′	Bp (mm), °C	n_D (t, °C)	d_4 (t, °C)	% yield
CH_3	—CH=$C(CH_3)_2$	50 (0.5)	1.5314 (19.6)	0.906 (19.6)	23
CH_3	—$C(CH_3)$=$C(CH_3)_2$	58 (0.4)	1.5292 (20.3)	0.915 (20.3)	..
n-C_3H_7	—CH=$C(CH_3)_2$	88 (0.5)	1.5172 (20.8)	0.891 (20.8)	..

b. $CH_3CO(CH{=}CH)_nCl$

n	Bp (mm), °C	n_D (t, °C)	d_4 (t, °C)
1	37 (15)	1.4672 (17.8)	1.126 (17.8)
2	53 (15)	1.5205 (18.5)	1.106 (18.5)

c. RCOCH=CH—Ar

R	Ar	Bp (mm), °C	[mp, °C]	% yield	Ref
CH_3	2,4$(CH_3)_2$-C_6H_3	145–146 (8)	[32]	64.2	184
CH_3	2,5$(CH_3)_2$-C_6H_3	130 (4–4.5)		20	184
CH_3	2,4,6$(CH_3)_3$-C_6H_2		[65–66]	61	184
CH_3	p-$CH_3OC_6H_4$		[72–74]	54	169
CH_3	2,4-$(CH_3O)_2$-C_6H_3	200–220 (7)	[62]	14	169
CH_3	2,5-$(CH_3O)_2$-C_6H_3		[57-58]	12.5	169
CH_3	2-(CH_3O)-5-(CH_3)-C_6H_3	157–167 (5)	[33]	41.5	169
CH_3	C_4H_3S	117–117.5 (4)	[22.5–23]	39	169
C_2H_5	p-$C_2H_5OC_6H_4$		[64–65]	55.6	169
n-C_3H_7	p-$CH_3OC_6H_4$	159–162 (2)	[37]	57	169
n-C_5H_{11}	p-$CH_3OC_6H_4$		[42–43]	62	169
$ClCH_2$	C_6H_5	138–139 (5)	[62]	79	184
$ClCH_2$	o- + p-$CH_3C_6H_4$		[49–52]	83.7	184
$ClCH_2$	2,5-$(CH_3)_2$-C_6H_3		[98–100]	74.8	184
$ClCH_2$	2,4-$(CH_3)_2$-C_6H_3		[70–71]	50	184
$ClCH_2$	o- + p-ClC_6H_4		[70–80]	10.7	184
C_6H_5	2,4,6-$(CH_3)_3$-C_6H_2		[95]	56.6	184
o-ClC_6H_4	p-$C_2H_5OC_6H_4$		[83]	65.5	14
o-ClC_6H_4	3,4-$(CH_3O)_2C_6H_3$		[102]	50.6	14
o-ClC_6H_4	2,5-$(CH_3O)_2C_6H_3$		[115]	50	14
o-ClC_6H_4	p-$CH_3OC_6H_4$		[77]	51	14
p-$NO_2C_6H_4$	p-$CH_3OC_6H_4$		[175–176]	52.6	14
p-$NO_2C_6H_4$	p-$C_2H_5OC_6H_4$		[155–156]	47.4	14
p-BrC_6H_4	2-(CH_3O)-5-(CH_3)-C_6H_3		[91]	50	14

III. Ketones: Type RCOC(R′)=CHCl

A. PREPARATION

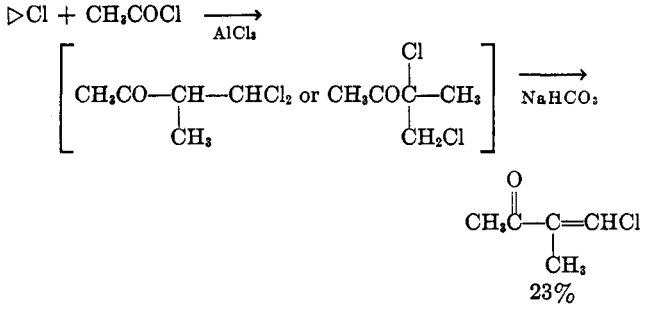
Chloromethylene ketones of this type are best prepared by the addition of thionyl chloride to the corresponding hydroxymethylene ketones in ether.

$$R{-}CO{-}\underset{\underset{CHOH}{\|}}{C}{-}R' + SOCl_2 \longrightarrow RCO{-}\underset{\underset{CHCl}{\|}}{C}{-}R' + HCl + SO_2$$

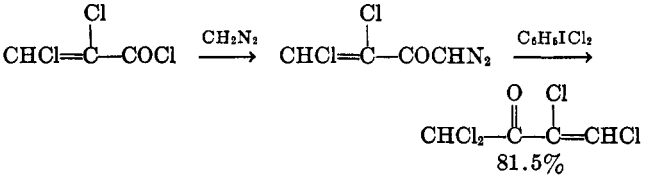
This appears to be the only general method known for the synthesis of these compounds at the present time. The method was found to be quite successful for the

synthesis of chloromethylenecycloheptanone and chloromethylenecyclooctanone, but failed with hydroxymethylenecyclopentanone and hydroxymethylenecyclohexanone where the chloromethylene ketone products appear to be too unstable to isolate by normal procedures (16).

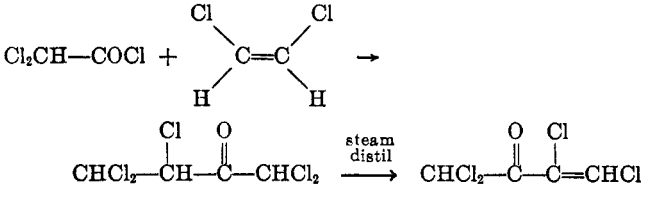
Hart and Levitt (45) prepared 1-chloro-2-methyl-1-buten-3-one through treatment of chlorocyclopropane with acetyl chloride in the presence of aluminum chloride and then with 10% sodium bicarbonate. The intermediate dihalo ketone was not isolated.



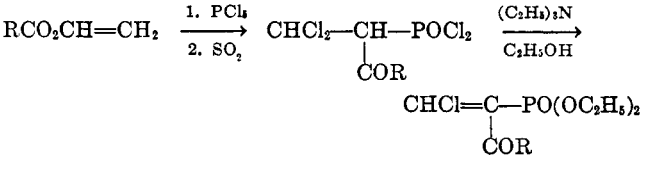
Roedig and Kloss (203) treated α,β-dichloroacrylyl chloride with diazomethane to obtain the corresponding diazo ketone which on treatment with iodobenzene dichloride formed 1,2,4,4-tetrachloro-1-buten-3-one.



The same compound has been prepared through the addition of dichloroacetyl chloride to *cis*-1,2-dichloroethylene (199).



Finally, Lutsenko, Kirilov, and Ovchinnikova (145, 146) have obtained α-phosphorylated β-chlorovinyl ketones through the addition of phosphorus pentachloride to vinyl esters followed by treatment of the intermediate with triethylamine in alcohol.



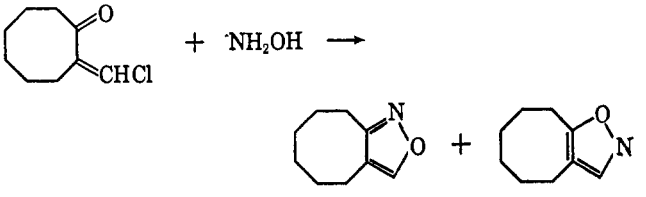
The α-phosphorylated β-chlorovinyl ketones have a considerably less mobile β-chlorine atom than that observed for the β-chlorovinyl ketones discussed in section II (145, 146).

The β-chlorovinyl ketones prepared by these various methods are listed in Table XXVII.

B. CHEMICAL AND PHYSICAL PROPERTIES

Noncyclic compounds of this type decompose slowly on storage. 1-Chloro-2-methyl-1-buten-3-one exhibits maximal absorption in the ultraviolet in 95% ethanol at 234 mμ (ϵ 1790) (45), indicating either a nonplanar or *cisoid* conformation. It does, however, react in much the same manner as the β-chlorovinyl ketones discussed in section II. Thus it readily forms a 2,4-dinitrophenylhydrazone (mp 204–205°) and a semicarbazone (mp 181.5°). Lithium aluminum hydride reduction leads to the corresponding carbinol in 90% yield. With hydrogen and a platinum catalyst, however, both the double bond and the carbonyl group are reduced with concomitant displacement of the β-chlorine atom (45).

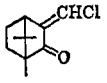
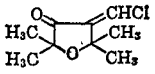
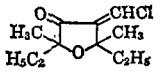
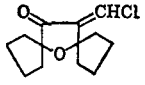
The cyclic β-chlorovinyl ketones of this type are unique, since they represent a fixed *cisoid* system. This is reflected in the ultraviolet by relatively low absorption maxima when compared with the *transoid* β-chlorovinyl ketones discussed in section II. Thus chloromethylenecycloheptanone absorbs maximally in 95% ethanol at 244.5 mμ (ϵ 4100), whereas chloromethylenecyclooctanone absorbs maximally at 247 mμ (ϵ 8300) (16). These two compounds on treatment with trimethylamine form the corresponding quaternary salts in good yields. Treatment of these cyclic chloro ketones with hydroxylamine yields the same mixture of isoxazoles obtained through the addition of hydroxylamine to the corresponding hydroxymethylene ketones



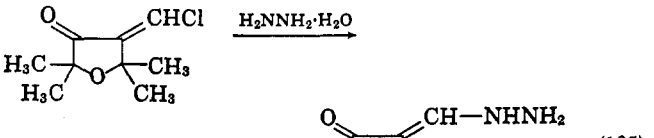
(4, 22). Thus both addition of hydroxylamine to the carbonyl group and replacement by hydroxylamine of the β-chlorine atom occur readily. Chloromethylenecyclooctanone also forms a solid derivative with 2,4-dinitrophenylhydrazine, mp 180–181° (16).

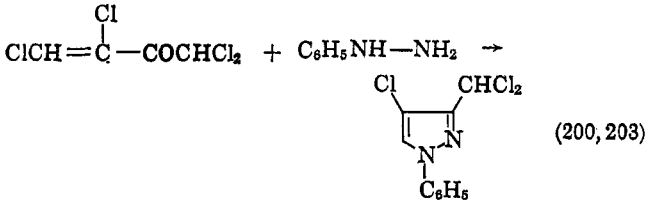
The β-chlorine atom thus appears to be easily replaced. In other examples, Rupe and Iselin (205) found that Grignard reagents react readily in high yields with chloromethylenecamphor, replacing the β chlorine by an alkyl group. Bishop, Claisen, and Sinclair (20) report the displacement of the β-chlorine atom by alkoxide and cyanide ion, while Kreutzkamp and Mengel (136) found that triethyl phosphite reacts to form the corresponding diethylphosphonomethylenecamphor in 81% yield. These reactions are summarized in Scheme VII.

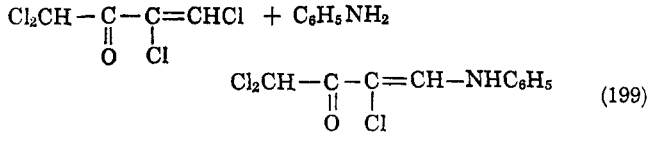
TABLE XXVII
β-CHLOROVINYL KETONES: TYPE RCOC(R′)=CHCl

R	R′	Bp (mm), °C [mp, °C]	n_D (t, °C)	d_4 (t, °C)	% yield	Ref
CH_3	CH_3	32–36 (3)	1.4694–1.4704 (25)	...	23	45
i-C_4H_9	CH_3	68–70 (7)	1.4573 (20)	0.9892 (20)	75	87
$CHCl_2$	Cl	90–92 (11)	1.5885 (20)	1.5300 (25)	59	199, 203
CHN_2	Cl	[53]	...	...	81.5	203
$-(CH_2)_5-$		101-102 (12)	1.5105 (22)	1.1339 (20)	80	16, 220
$-(CH_2)_6-$		93 (2)	1.5140 (20)	...	91.8	16
		113 (12.5)	...	0.8946 (20)	95	205
		[81]	...	...	80	135
		90–91 (7)	1.4792 (20)	1.1200 (20)	71	135
		109–111 (2)	1.5219 (20)	1.1704 (20)	67	135
CH_3	$-PO(OC_2H_5)_2$	102–103 (2)	1.4645 (20)	1.1861 (20)	88	145
C_2H_5	$-PO(OC_2H_5)_2$	117 (1.5)	1.4670 (20)	1.1604 (20)	78.6	146
n-C_3H_7	$-PO(OC_2H_5)_2$	122–123 (1)	1.4656 (20)	1.1355 (20)	61	146

There are, in addition, several examples of substitution of the β chlorine by amines as illustrated below.





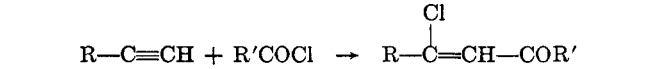


IV. KETONES: TYPE RCOCH=C(R′)Cl

A. R′ REPRESENTS AN ALKYL OR ARYL GROUP

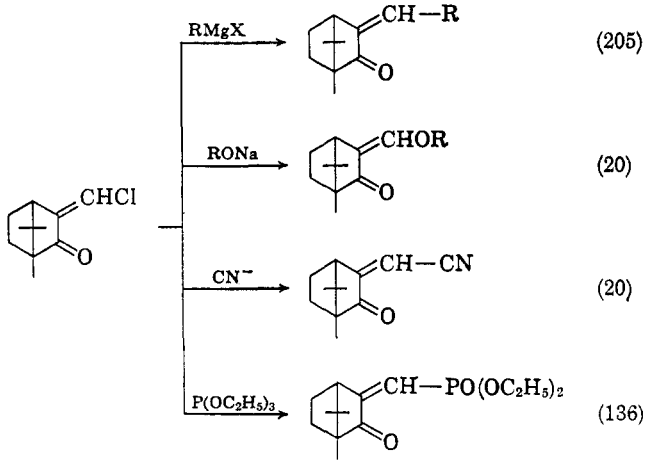
1. *Preparation*

Compounds of this type may be prepared conveniently by the addition of acyl halides to alkyl or aryl acetylenes in the presence of a Friedel-Crafts catalyst (Table XXVIII).

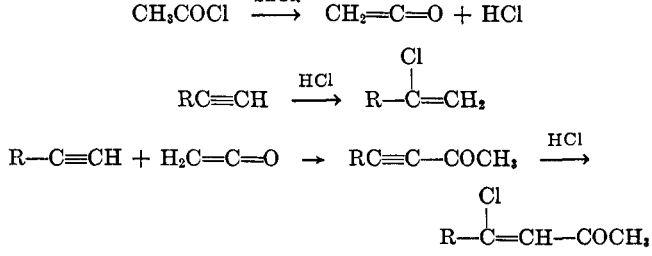


Kroeger, Sowa, and Nieuwland (138) found stannic chloride to give the best results. The acid chloride

SCHEME VII



itself is used as the solvent although solvents such as CCl_4, CS_2, etc., may be used equally well. Since a small amount of chloroolefin was formed as a side product, the following mechanism was suggested.



Both *cis*- and *trans*-β-chlorovinyl ketones were formed in this reaction and could be separated through fractional distillation. More evidence is necessary to prove this mechanism. The structure of the *trans* isomer was

TABLE XXVIII
β-CHLOROVINYL KETONES: TYPE RCOCH=C(R')Cl

R	R'	Bp (mm), °C [mp, °C]	n_D (t, °C)	d_4 (t, °C)	% yield	Ref
CH_3	CH_3	42 (11)	1.4641 (20)		57.6	48, 66
CH_3	C_2H_5	46–53 (10)			25–40	138
CH_3	n-C_3H_7	*trans* 54.5–55.5 (10)	1.4702 (23)	1.0134 (23)		
		cis 62–63 (10)	1.4602 (23)	1.0321 (23)	25–40	138
CH_3	n-C_4H_9	*trans* 69 (10)	1.4675 (25)	0.9705 (25)		
		cis 80 (10)	1.4721 (25)	0.9984 (25)	37	138
CH_3	n-C_5H_{11}	*trans* 89 (10)	1.4665 (25)	0.9752 (25)		
		cis 99 (10)	1.4607 (25)	0.9830 (25)	25–40	10, 11, 138
C_2H_5	n-C_3H_7	39–41 (0.03)	1.4696 (24)	0.999 (20)		150
n-$C_3H_7CH(C_2H_5)$	CH_3				78.5	48
CH_3	C_6H_5	137-138 (10)	1.5930 (20)	1.2373 (20)		10, 11
C_6H_5	CH_3				67	48
$-(CH_2)_2-$		Semicarbazone 235–237 dec				158, 159
$-(CH_2)_3-$		87–88 (15)	1.5008 (25)	1.181 (25)	...	27, 158, 159
$-CH_2C(CH_3)_2CH_2-$		78 (7)	1.4953 (22)	...	79	34, 35, 40, 211
$-CH_2C(CH_2)_5CH_2-$		167 (30) [47]	...	...		188
$-CH_2CH(CHMe_2)CH_2-$		126–130 (14)	...	...	69	56
$-CH(CHMe_2)CH_2CH_2-$		93 (4)	...	...	55.7	6
CH_3	Cl	153–156 (760)	1.4928 (20)	1.3098 (20)	80	71, 207, 224
C_2H_5	Cl	64–64.5 (12)	1.4909 (18.5)	1.2463 (18.5)	46	33
n-C_3H_7	Cl	88–89 (18)	1.4844 (20.5)	1.1751 (20.5)	65	33
i-C_3H_7	Cl	76 (14)	1.4845 (20)	1.1751 (20.5)	78	215
n-C_5H_{11}	Cl	95–96 (10)	1.4830 (20)	1.1218 (20)	60	33
$CHCl_2$	Cl	89–93 (12)	1.5385 (19)	...	6.8	215
C_6H_5	Cl	144.5–145.5 (15)	1.5942 (20)	1.3130 (20)	79	33, 65
$C_6H_5CH_2CH_2$	Cl	156–157 (11) [40.5–42]	...	...	61	33
o-HOC_6H_4	Cl	132–134 (5) [55–56]	...	...	40	143
p-HOC_6H_4	Cl	[109–110]	...	...	38	143
2-HO-5-CH_3-C_6H_3	Cl	142–144 (5) [92–93]	...	...	78	143
p-ClC_6H_4	Cl	168–169 (8) [51–52]	...	...		228
p-$NO_2C_6H_4$	Cl	[108–109]	...	...	11.4	215

elucidated by preparing the same isomer through the addition of hydrogen chloride to the corresponding acetylenic ketone.

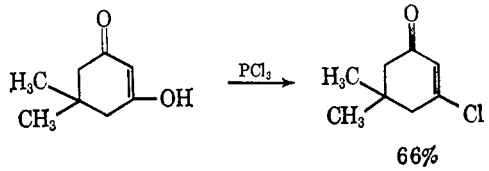
Belov and Shekhtman (11) investigated the addition of acetic anhydride to alkyl and aryl acetylenes in the presence of zinc chloride. Again no solvent was used.

Henry (48) has patented a process whereby β-alkyl and β-aryl β-chlorovinyl ketones may be prepared through the addition of acid chlorides to propadiene in the presence of a Friedel-Crafts catalyst in inert solvents such as CCl_4, $CHCl_3$, CH_2Cl_2, etc. The reaction is run at −5 to 15°, and yields are usually 40–70%.

Julia (66) found that acetyl chloride reacts with 2-chloropropene in the presence of aluminum chloride to form a dichloro ketone, which on steam distillation eliminates hydrogen chloride to form 4-chloro-3-penten-2-one in 57.6% yield.

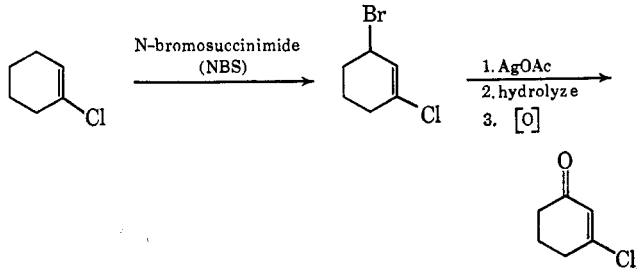
$$CH_3C(Cl)=CH_2 + CH_3COCl \rightarrow CH_3C(Cl)_2CH_2COCH_3 \rightarrow CH_3C(Cl)=CHCOCH_3$$

Cyclic β-chlorovinyl ketones are easily prepared from cyclic β-diketones, by refluxing the diketone in chloroform with phosphorus trichloride (35). The yields are usually very good. Other reagents such as phosgene (211), acetyl chloride (56), thionyl chloride (40), and phosphorus oxychloride (35, 192) have also been used to effect this conversion.

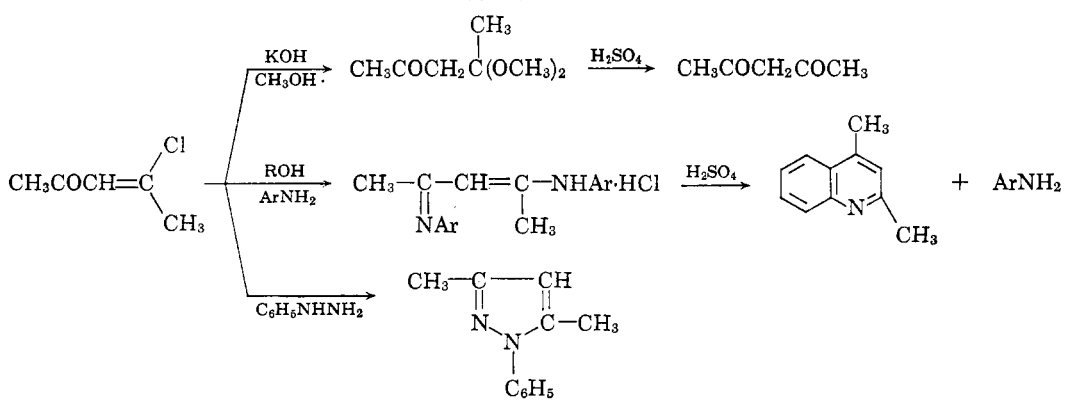


66%

Finally, 1-chloro-1-cyclohexen-3-one and 1-chloro-1-cyclopenten-3-one have been prepared in the following way (156–159).



SCHEME IX



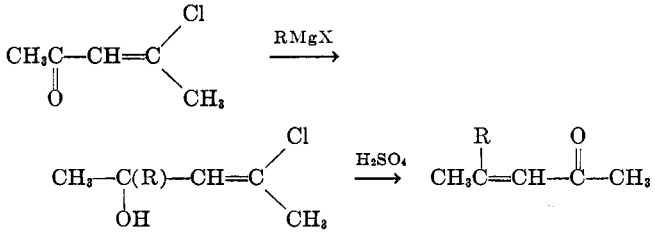
2. Physical Properties

β-Alkyl β-chlorovinyl ketones are pleasant smelling, high-boiling liquids; the cyclic compounds have a slight odor of peppermint. They are moderately lachrymatory and appear to have a minor vesicant action. The compound 2-chloro-2-penten-4-one exhibits maximal absorption in the ultraviolet at 245 mμ (ε 2750) (66), indicating a conjugated system, but one in which either a *cisoid* or nonplanar conformation is present. In a fixed *transoid* system of this type, *i.e.*, 3-chloro-5,5-dimethyl-2-cyclohexen-1-one, absorption occurs at 238 mμ and with much greater intensity (ε 13,500) (17).

3. Chemical Properties

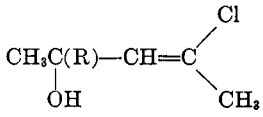
The β-alkyl β-chlorovinyl ketones are slightly unstable and darken on standing. Their reactions have not been studied extensively, but they appear to be more stable than the β-chlorovinyl ketones discussed in section II. Thus they readily form the corresponding oximes (11, 17) and semicarbazones (11, 138). The fact that the oximes do not cyclize to form isoxazoles indicates that the β chlorine is more difficult to remove as would be expected of *cisoid* or nonplanar structures. However, the β-chlorine atom is labile as shown by the reactions (66) in Scheme IX.

Treatment of 2-chloro-2-penten-4-one with sodium alkyls or with Grignard reagents leads to the expected carbinols (66) (see Table XXIX). The utility of this reaction lies in the fact that these carbinols rearrange in high yields in 3% sulfuric acid to form α,β-unsaturated ketones (66, 67).



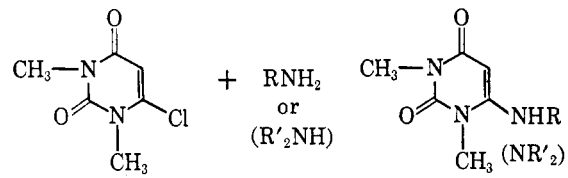
The cyclic β-chlorovinyl ketones appear to have been studied more thoroughly. The reactions of 5-substituted 3-chloro-2-cyclohexen-1-ones are illustrated in Scheme X.

TABLE XXIX (66)



R	Bp (mm), °C	n_D (t, °C)	% yield
H—C≡C—	40 (0.8)	1.4840 (20)	34.2
n-C_5H_{11}C≡C—	82 (0.19)	1.4843 (17)	60
CH_3	62 (15)	1.4560 (19)	44
C_2H_5	72 (14)	1.4689 (19)	73.5
$C_6H_5CH_2$	90–92 (0.1)	1.5390 (18)	60.3
C_6H_5	90–91 (3)	1.5660 (20)	63

Treatment with zinc and potassium iodide effectively removes the β-chlorine substituent (40). Sodium in ethanol reduces both the double bond and the carbonyl group, removing the β-chlorine atom as well (56, 188). In the case of the 5-isopropyl analog, the alcohol formed was shown to be 94% *cis* and 6% *trans* (56). Zinc and glacial acetic acid on the 5,5-pentamethylene analog resulted in reduction of the double bond and removal of the β-chlorine substituent, affording the ketone in 86% yield (188). Hydrogenation over palladium or Raney nickel usually reduces the double bond and removes the chlorine atom too (6, 40, 214). Lithium aluminum hydride reductions were unsuccessful; no reaction apparently occurred. These compounds usually add 2 moles of amine (46). However, 1,3-dimethyl-4-chlorouracil was found to react with amines very easily (192).

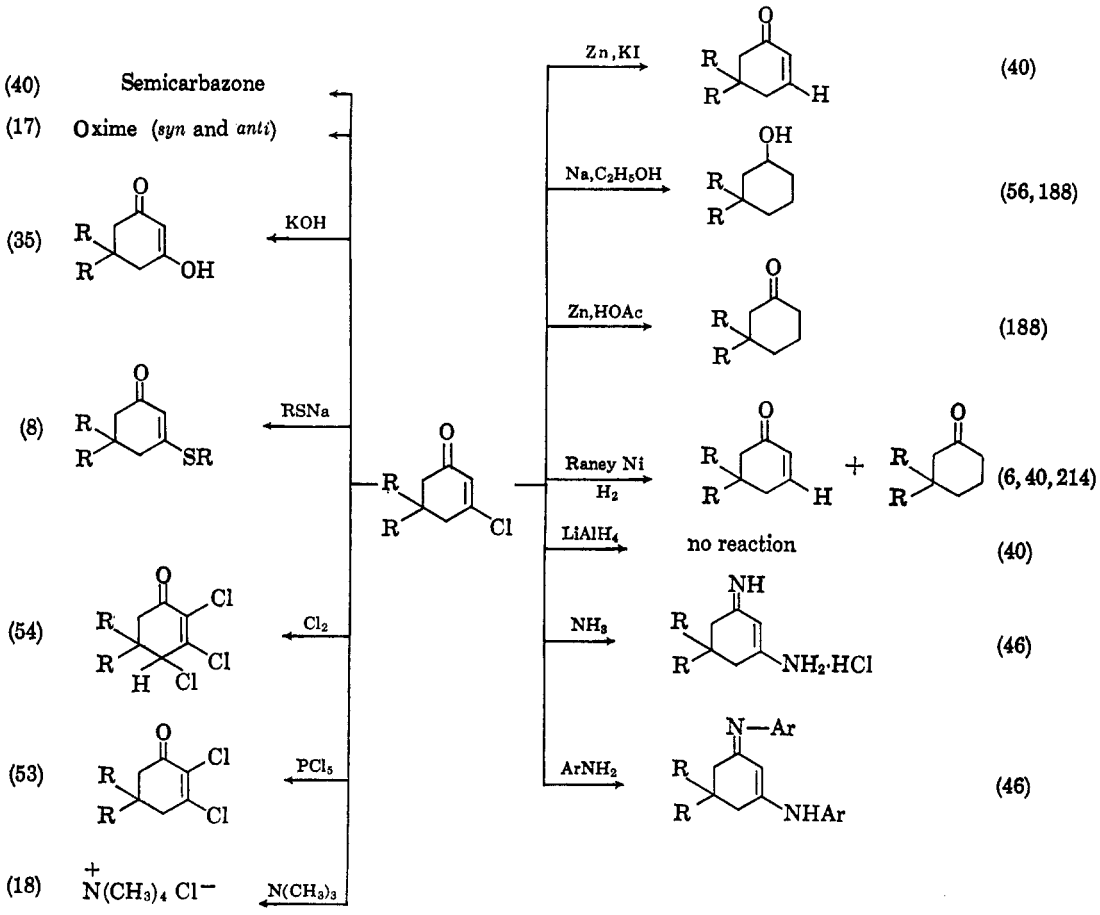


R=CH_3, C_2H_5, *n*-C_4H_9, CH_2CH_2OH

R′=CH_3

Finally, the sodium salt of methyl mercaptan cleanly displaces the β-chlorine atom of 3-chloro-2-cyclohexen-1-one (8).

SCHEME X



B. R′ REPRESENTS A CHLORINE ATOM ($RCOCH{=}CCl_2$)

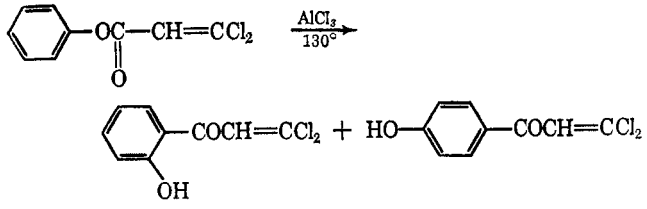
1. Synthesis

The most general method of synthesis of these β,β-dichlorovinyl ketones (see Table XXVIII) involves the addition of acid chlorides to 1,1-dichloroethylene in the presence of a Friedel-Crafts catalyst (33, 215). The

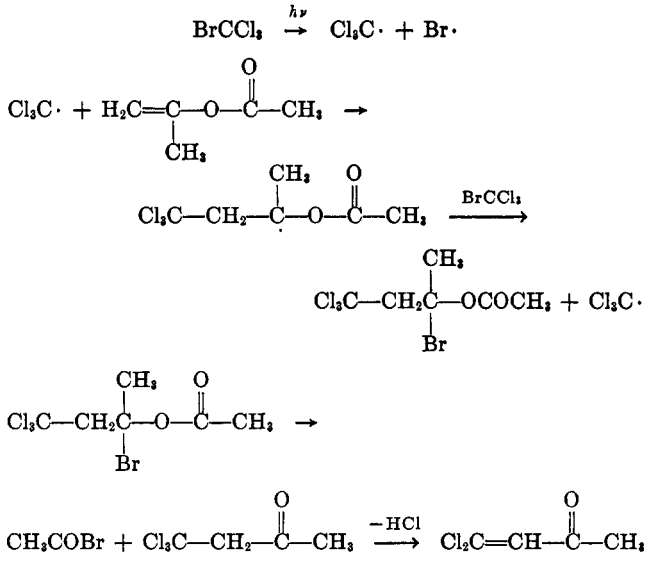
$$RCOCl + CH_2{=}CCl_2 \rightarrow RCOCH{=}CCl_2$$

yields by this method are usually very good.

There are, however, several other methods which have appeared in the literature, but which have not been widely used. Thus Coq, Levas, and Levas (33) have prepared the phenyl esters of β,β-dichloroacrylic acids and treated them with aluminum chloride. Under these conditions a Fries rearrangement occurs leading to the formation of β,β-dichlorovinyl aryl ketones.



Isopropenyl acetate was condensed with bromotrichloromethane under free-radical conditions to form methyl β,β-dichlorovinyl ketone (71). The mechanism proposed for this reaction was



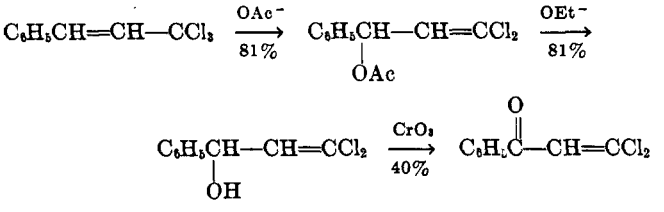
Sanchez (207) prepared phenyl β,β-dichlorovinyl ketone in the following way.

TABLE XXX

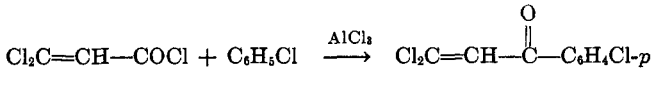
REACTIONS OF β,β-DICHLOROVINYL KETONES

Ketone RCOCH=CCl₂ R	Reactant	Product RCOCH=CX₂ X	Bp (mm), °C	[mp, °C]	nD (t, °C)	% yield	Ref
CH_3	CH_3NH_2	CH_3NH		[227–228]	...	89	207
CH_3	$(CH_3)_2NH$	$(CH_3)_2N$	58.5 (0.05)		...	90	207
CH_3	$(CH_2)_5NH$	$(CH_2)_5N$	118–122 (0.03)	[76.0–77.5]	...	93	215
CH_3	$C_6H_5NH_2$	C_6H_5NH		[116–117.5]	...	98	215
CH_3	p-$ClC_6H_4NH_2$	p-ClC_6H_4NH		[161–162]	...	92	215
i-C_3H_7	$(CH_2)_5NH$	$(CH_2)_5N$		[79.5–81.0]	...	68	215
i-C_3H_7	$(C_2H_5)_2NH$	$(C_2H_5)_2N$	66–70 (0.02)		1.4965–1.4975 (20)	53	215
i-C_3H_7	$C_6H_5NH_2$	C_6H_5NH		[102–103]	...	74	215
i-C_3H_7	o-$CH_3C_6H_4NH_2$	o-$CH_3C_6H_2NH$		[104–105]	...	78	215
Cl_2CH	$C_6H_5NH_2$	C_6H_5NH		[143–144]		70	215
C_6H_5	$(CH_2)_5NH$	$(CH_2)_5N$		[85.5–87]	...	86	215
C_6H_5	$(n$-$C_4H_9)_2NH$	$(n$-$C_4H_9)_2N$	155 (0.01)		1.5535–1.5542 (16)	85	215
C_6H_5	$C_6H_5NH_2$	C_6H_5NH		[127–129]	...	98	215
C_6H_5	$H_2NCH_2CH_2NH_2$	$-CH_2NH-$		[204–214]	...	69	207
C_6H_5	$(CH_3)_2NH$	$(CH_3)_2N$	130–134 (0.04)		...	78	207
CH_3	C_6H_5OH	C_6H_5O	133 (0.03)			78	207
CH_3	o-HOC_6H_4OH	o-HOC_6H_4O		[105–105.5]		43	207
CH_3	o-$CH_3OC_6H_4OH$	o-$CH_3OC_6H_4O$		[115–116]		47	207
C_6H_5	C_6H_5OH	C_6H_5		[117–119]		65	207
C_6H_5	o-HOC_6H_4OH	o-HOC_6H_4O		[151–152]		56	207
CH_3	C_6H_5SH	C_6H_5S		[98–99]		98	207
C_6H_5	C_6H_5SH	C_6H_5S		[139–140]		55	207
CH_3	HI	I		[50–53]		84	207
C_6H_5	HI	I		[74–75.5]		35	207
CH_3[a]	CH_3ONa	CH_3O	135–136.5 (20)		1.4738 (19)	..	66, 177, 207
CH_3	C_2H_5ONa	C_2H_5O	114.5–115 (11)		1.4915 (19)	..	66, 177, 207
		$RR'C(OH)-CH=CCl_2$ R	R′				
CH_3	$NaBH_4$	CH_3	H			82	207
C_6H_5	$NaBH_4$	C_6H_5	H			96	207
p-Cl-C_6H_4	$Al(i$-$C_3H_7O)_3$	p-ClC_6H_4	H			..	228
CH_3[b]	CH_3MgI	CH_3	CH_3	63 (13)	1.4814 (19)	55	47
CH_3	C_2H_5MgBr	CH_3	C_2H_5	77–78 (14)	...	52	224
CH_3	n-$C_4H_9C{\equiv}CMgBr$	CH_3	n-$C_4H_9C_2$	90 (0.5)	1.4909 (20)	85	47
CH_3	$BrMgC{\equiv}CMgBr$	CH_3	$-C{\equiv}C-$	[98]	...	15	47

[a] d^{19}_4 1.002. [b] d^{20}_4 1.2220.



Finally, β,β-dichloroacrylyl chloride has been condensed with chlorobenzene under Friedel–Crafts conditions to form the corresponding β,β-dichlorovinyl ketone (228).



2. *Physical Properties*

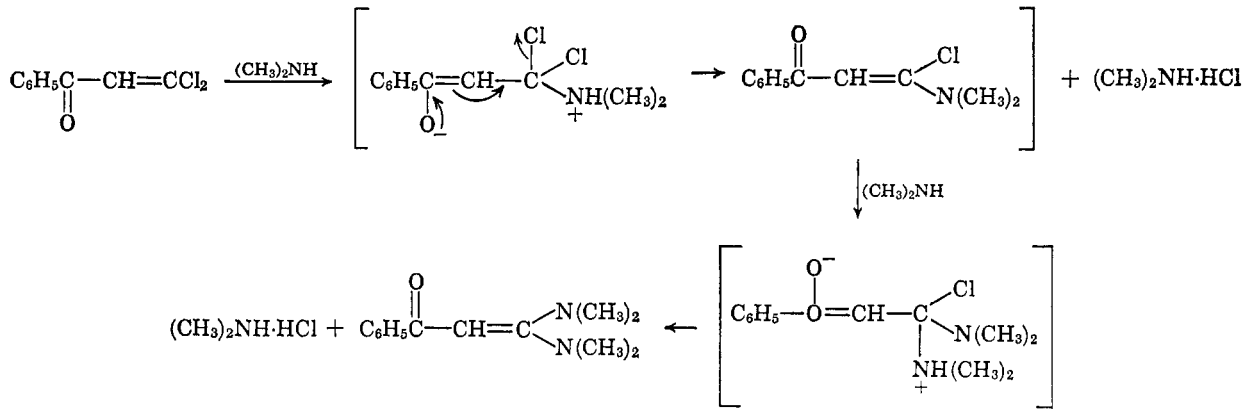
A careful study (207) of these β,β-dichlorovinyl ketones indicates coplanarity and extensive conjugation. Thus the infrared spectra of methyl and phenyl β,β-dichlorovinyl ketones show carbonyl bands at 5.88 and 6.00 cm^{-1}, respectively. The ultraviolet spectra in 95% ethanol exhibit intense bands at 241 (ε 11,900) and 263 mμ (ε 14,300), respectively. In addition, dipole moment data indicate, although not conclusively, that methyl β,β-dichlorovinyl ketone has a *transoid* configuration. On the other hand, phenyl β,β-dichlorovinyl ketone probably exists in the planar *cisoid* conformation (207).

These β,β-dichlorovinyl ketones are slightly unstable at room temperature but are considerably more stable when stored at 0°. The presence of water seems to inhibit decomposition. Thus methyl β,β-dichlorovinyl ketone when stored with a small amount of water for 6–9 months only turned very pale green (215).

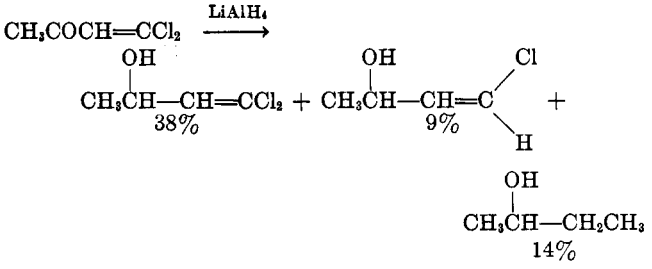
3. *Reactions of β,β-Dichlorovinyl Ketones*

The chemistry of β,β-dichlorovinyl ketones is analogous to that found with β-chlorovinyl ketones of the type

SCHEME XI

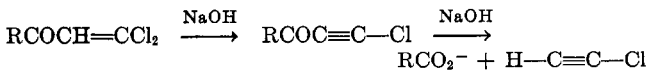


RCOCH=CHCl (section II), although it is not nearly as extensive (see Table XXX). These β,β-dichlorovinyl ketones readily react at the carbonyl group to form 2,4-dinitrophenylhydrazones (66) and semicarbazones (224). The addition of Grignard reagents again results in the corresponding β,β-dichlorovinylcarbinols in good yields (47, 66, 224). However, sodium acetylide did not react with methyl β,β-dichlorovinyl ketone (47). The carbonyl group is easily reduced with either aluminum isopropoxide (228) or with sodium borohydride (207) forming β,β-dichlorovinylcarbinols. Use of lithium aluminum hydride, however, results in mixtures of reduction products (207).



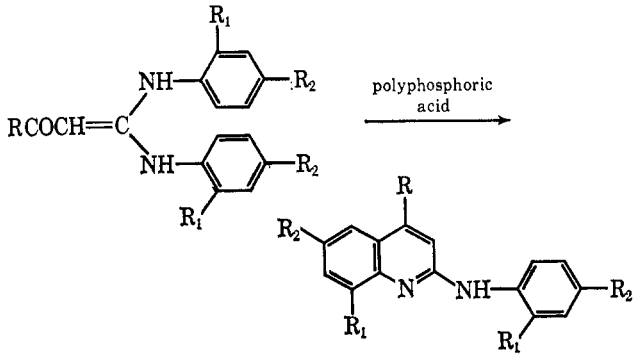
No simple addition reactions to the double bonds of these compounds have been recorded. They do not decolorize bromine in carbon tetrachloride solutions (66).

The hydrolysis of these compounds with dilute sodium hydroxide has been studied. The initial reaction appears to be formation of a β-chloroacetylenic ketone which subsequently is cleaved to chloroacetylene (207).



Nucleophilic replacements of either one or both of the β-chlorine atoms are known to occur with ease. Conclusive evidence for a conjugate addition process was supplied by Sanchez (207), who investigated the addition of tritiated amines to phenyl β,β-dichlorovinyl ketone. The total product activity was found to lie in the amine hydrochloride, thus eliminating the possibility of any addition–elimination, or elimination to an acetylenic ketone and then addition, mechanism (Scheme XI).

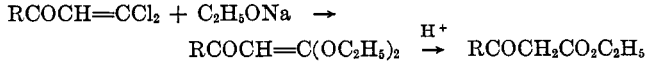
This reaction with amines occurs readily in some common solvents (ether, benzene, ethanol) in high yields (70–90%). Both aliphatic and aromatic primary amines react. Tertiary amines and hindered secondary amines gave mixtures from which no pure products could be isolated. The structures of the dianilino derivatives were proven by cyclization to the corresponding substituted 2-anilinoquinolines (215).



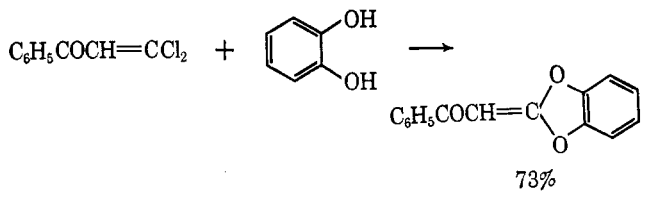
74–97%

Ammonia did not yield the expected β,β-diaminovinyl ketone. Instead a product believed to be 2,6-diphenyl-3-cyano-4H-pyran-4-one was isolated in 30% yield (207).

Aliphatic alcohols in the presence of sodium alkoxide react readily under anhydrous conditions to form β,β-dialkoxyvinyl ketones (66, 177, 207). These are hydrolyzed easily with dilute acid to β-keto esters.

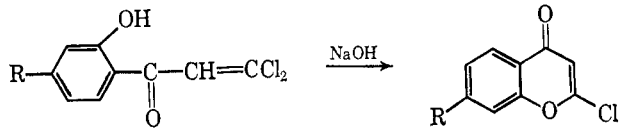


In a medium of anhydrous potassium carbonate suspended in acetone, phenols readily displace the β-chlorine atoms of β,β-dichlorovinyl ketones forming β,β-diphenoxyvinyl ketones. Under more vigorous conditions catechol reacts with phenyl β,β-dichlorovinyl ketone to form β,β-phenylenedioxyacrylophenone.

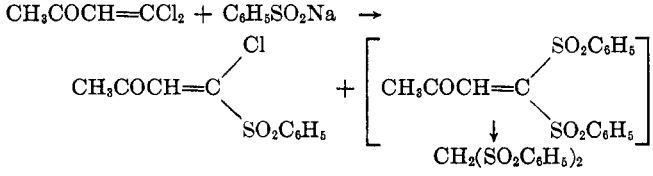


In the case of other difunctional aromatics, such as *o*-phenylenediamine, *o*-aminophenol, and *o*-aminobenzenthiol, only poorly defined mixtures of products were obtained (207).

Coq, Levas, and Levas (33) successfully cyclized *o*-hydroxy-β,β-dichloroacrylophenones to substituted chromones with dilute sodium hydroxide.

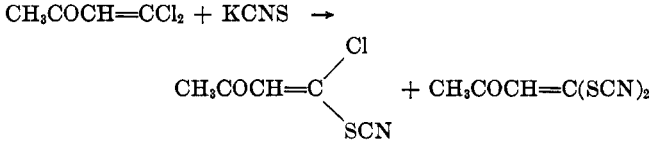


Various sulfur-containing compounds have been used to displace the β-chlorine atoms of β,β-dichlorovinyl ketones (207). Thus thiophenols react quite readily yielding β,β-dithiophenoxyvinyl ketones, whereas ethyl mercaptan yielded an inseparable mixture of products. Thiourea and phenylthiourea gave highly colored solids of unknown structure (207). Sodium benzenesulfinate reacted readily with replacement of one and then both of the β-chlorine substituents (177). The monosulfone was isolated in low yield; the disulfone undergoes fur-

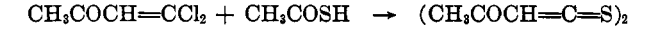


ther cleavage to diphenylsulfonylmethane.

Potassium thiocyanate likewise replaces first one and then both β-chlorine substituents and both products have been isolated (177).



Finally, thioacetic acid in potassium bicarbonate–methanol solution reacts with methyl β,β-dichlorovinyl ketone to form "dimeric acetylthioketone" (177).

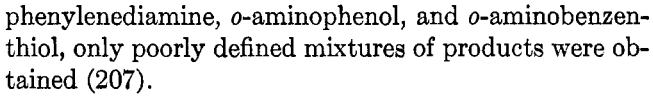


Attempted replacements of the β-chlorine atoms of β,β-dichlorovinylketones with cyanide ion were unsuccessful; the reaction results in intractable tars. Potassium iodide in acetone also failed to react. However, by using concentrated hydriodic acid at room temperature, it is possible to obtain the corresponding β,β-diiodovinyl ketones (207).

V. β-CHLOROVINYL KETONES: TYPE RCOC(R′)=C(R′)Cl

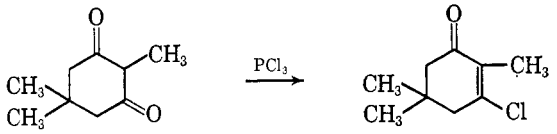
A. PREPARATION (TABLE XXXI)

A very general method for the synthesis of ketones of this type involves the addition of acid chlorides to dialkyl acetylenes in the presence of a Friedel-Crafts condensing agent (137, 138).

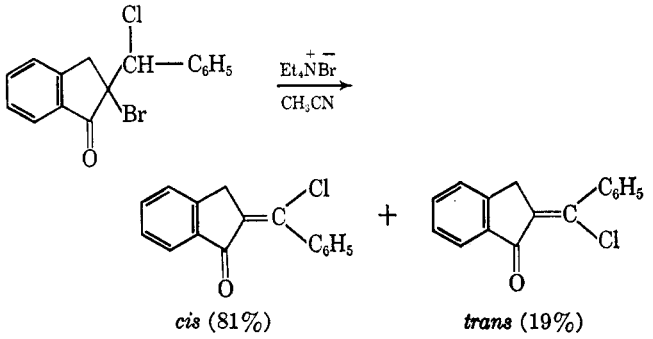


As in the case with monoalkylacetylenes, both *cis* and *trans* isomers are again produced and have been separated by fractional distillation.

Several ketones of this type also have been prepared by the treatment of cyclic β-diketones with phosphorus trichloride (44) or thionyl chloride (149).



Dehydrobromination of 2-bromo-2-(α-chlorobenzyl)-1-indanone with tetraethylammonium chloride in acetonitrile leads to the formation of both the *cis* and *trans* isomers of 2-(α-chlorobenzal)-1-indanone in 80% yield (70). The corresponding reaction in the tetralone series results in formation of the endocyclic rather than exocyclic product.



cis (81%) *trans* (19%)

It has been found that acyl halides condense readily with cyclopentanone to form 1-acyl-2-chlorocyclopentenes (127, 128). The reaction is best carried out by adding cyclopentanone to the acid chloride–alu-

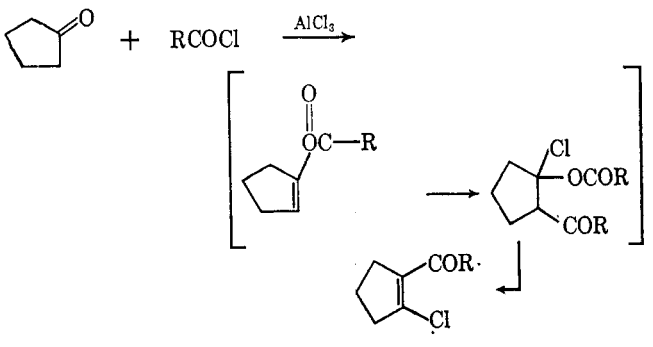


TABLE XXXI
β-CHLOROVINYL KETONES: TYPE RCOC(R′)=C(Cl)R″

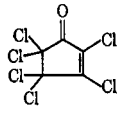
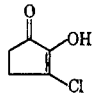
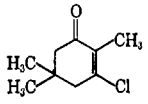
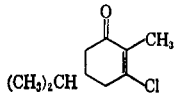
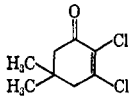
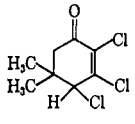
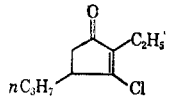
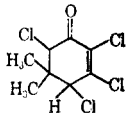
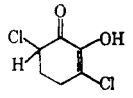
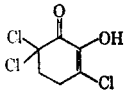
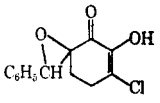
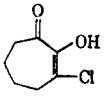
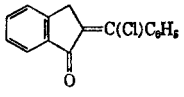
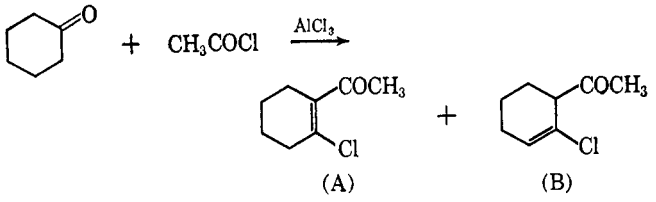
R	R′	R″	Bp (mm), °C [mp, °C]	n_D (t, °C)	d_4 (t, °C)	% yield	Ref
CH_3	C_2H_5	C_2H_5	*trans* 89–91 (30)	1.4611 (25)	0.9993 (25)	25–40	138
			cis 97–99 (30)	1.4596 (25)	1.0029 (25)	25–40	138
CH_3	n-C_3H_7	n-C_3H_7	*trans* 112–113 (28)	1.4601 (25)	0.9592 (25)	25–40	138
			cis 117–118 (28)	1.4587 (25)	0.9680 (25)	25–40	138
CH_3	n-C_4H_9	n-C_4H_9	140–146 (28)	1.4612 (25)	0.9459 (25)	25–40	138
CH_3	n-C_5H_{11}	n-C_5H_{11}	115–121 (5)	1.4626 (25)	0.9348 (25)	25–40	138
CH_3	$-(CH_2)_5-$		90–92 (22)	1.5045 (20)	1.1429 (20)	31	128, 156
C_2H_5	$-(CH_2)_5-$		97–98 (13)	1.4952 (20)	1.1000 (20)	37	128
n-C_3H_7	$-(CH_2)_5-$		106–107 (8)	1.4900 (20)	1.0746 (20)	38.2	128
i-C_4H_9	$-(CH_2)_5-$		74–75 (2)	1.4835 (20)	1.0360 (20)	36	128
CH_3	$-(CH_2)_4-$		93–98 (9)	1.4952 (25)	1.1187 (25)	...	27
C_2H_5	$-(CH_2)_4-$		113–116 (12)	1.4901 (25)	1.0931 (20)	...	27
n-C_3H_7	$-(CH_2)_4-$		126 (12)	1.4879 (25)	1.0702 (25)	...	27
$CH_3(CH_2)_4CH(C_2H_5)$	$-(CH_2)_4-$		135–140 (3)	1.472 (25)	0.975 (25)	...	27
$CH_3CH=CH$	$-(CH_2)_4-$		90–93 (0.15)	1.5171 (25)	1.1098 (20)	...	27
C_6H_5	$-(CH_2)_4-$		126 (0.14)	1.5717 (25)	1.178 (25)	...	27
CH_3	Cl	Cl	64–65 (17)	1.5110 (20)	1.4630 (20)	79	1
C_2H_5	Cl	Cl	78.5–79.5 (18)	1.5022 (18)	1.3786 (18)	48	33
n-C_3H_7	Cl	Cl	80.5–82 (12)	1.4960 (19.5)	1.3176 (19.5)	67	33
n-C_5H_{11}	Cl	Cl	104.5–106 (10)	1.4892 (20)	1.2117 (20)	50	33
$CHCl_2$	Cl	Cl	97–98 (12)	1.5424 (20)	1.696 (20)	70	201, 204
CH_2Cl	Cl	Cl	91 (12) [29]	...	...	95	204
CH_2OCOCH_3	Cl	Cl	120 (13)	1.5156 (20)	1.515 (20)	43	204
CH_2Br	Cl	Cl	101–102 (12)	1.5676 (20)	1.891 (20)	90	204
			53 (0.03) [28]	...	...	60	198
			[138]	...	...	70	49, 72
			78–80 (2)	1.4963 (22)	...	68	214
			121.5–124.5 (11)	1.5037 (20)	1.079 (20)	67	40
			[63]	...	...	...	53
			[61]	...	...	...	54
$CHBr_2$	Cl	Cl	133–135 (15)	1.5899 (20)	2.179 (20)	70	204
$Cl_2C=CCl$	Cl	Cl	94–95 (0.6)	1.5682 (15)	...	58.3	202
C_6H_5	Cl	Cl	135–137 (10)	1.5826 (21.5)	1.3965 (21.5)	86	21, 33
$C_6H_5CH_2CH_2$	Cl	Cl	154–155 (10)	1.5633 (21)	1.3320 (21)	45	33
p-ClC_6H_4	Cl	Cl	159 (17) [19]	...	...	...	21
p-$CH_3C_6H_4$	Cl	Cl	147.5 (10)	1.5787 (25)	1.3472 (25)	80	21
2,4-$(CH_3)_2C_6H_3$	Cl	Cl	165 (14)	...	...	...	21
2,5-$(CH_3)_2C_6H_3$	Cl	Cl	161 (13)	...	...	...	21
4-(i-C_3H_7)C_6H_3	Cl	Cl	173 (12)	...	...	...	21
2,4,5-$(CH_3)_3C_6H_2$	Cl	Cl	[57]	...	...	...	21
p-$CH_3OC_6H_4$	Cl	Cl	[26.5]	...	...	...	21
p-$C_2H_5OC_6H_4$	Cl	Cl	[58]	...	...	...	21

Table XXXI (*Continued*)

R	R′	R″	Bp (mm,°C) [mp, °C]	n_D (t, °C)	d_4 (t, C)	% yield	Ref
CH_3	CH_3	Cl	64–69 (15)	1.4822 (20)	1.253 (27)	33	215
C_6H_5	CH_3	Cl	78–79 (0.06) [<−5]	1.568 (20)	...	54	207
CH_3	$C_6H_5CH(OAc)$	Cl	122–126 (2)	1.5420 (24)	...		55
C_2H_5	Br	Cl	79–80 (11)	1.5201 (20)	1.6483 (20)	50	33
n-C_3H_7	Br	Cl	95–96.5 (14)	1.5120 (20.5)	1.5519 (20.5)	55	33
n-C_5H_{11}	Br	Cl	113–114.5 (10)	1.5054 (20)	1.4251 (20)	56	33
C_6H_5	Br	Cl	142–143 (10)	1.6025 (21.5)	1.6437 (21.5)	76	33
$C_6H_5CH_2CH_2$	Br	Cl	167–168 (10)	1.5742 (21)	1.5192 (21)	45	33
			88 (7)	...	...	...	149
			[91]	...	...	...	54
			[123]	...	...	64	31, 50, 217
			[96–98]	...	...	75	217
			[115–116]	...	...	59	217
			[128]	...	...	83	217
			80–82 (0.001)	...	...	66	51
			*cis* [70–71.5] *trans* [105–106.5]	...		80 {(81% *cis* 19% *trans*)	70

minum chloride complex in 1,2-dichloroethane. In the case of acetyl chloride, the reaction is thought to occur *via* addition of acetyl chloride to an enol acetate intermediate. The position of the double bond was shown by ozonolysis to glutaric acid. If the isomeric 1-acyl-2-chloro-2-cyclopentenes had formed, the product of oxonolysis would have been δ-ketocaproic acid. The ultraviolet absorption spectra of the 2,4-dinitrophenylhydrazones also indicate conjugation.

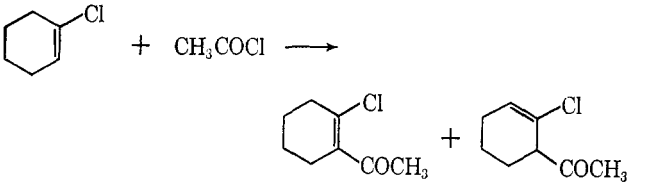
There is in the patent literature a report (27) that cyclohexanone reacts in an analogous manner. However, Jacquier and Brun (62) reports that the *sole* product of this reaction is the isomeric 1-acyl-2-chloro-2-cyclohexenes, which on refluxing with dimethylaniline yields 1-acetyl-2-chloro-1-cyclohexene. The latter isomerization, however, could not be repeated (127). Studies of the reactions (127, 129, 130) show that a mixture of both isomers was formed. This was based on the fact that treatment with semicarbazide gave two semicarbazones. The semicarbazone (mp 158°) isolated in greatest amount was shown to be that of ketone B.



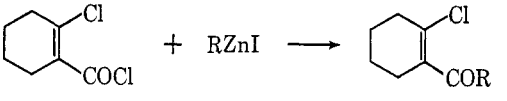
Only a small amount of the semicarbazone of ketone A was found. The 2,4-dinitrophenylhydrazone of B was prepared, and its ultraviolet spectrum also indicated that B was not conjugated. The reasons for this difference in the reactions of cyclopentanone and cyclo-

hexanone are not clear, although they are undoubtedly directly connected to the differences in conformation in the two rings.

Several other workers have prepared these compounds by different paths. Cyclohexene was condensed (10) with acetic anhydride in the presence of zinc chloride to yield a mixture of 1-acetyl-2-chloro-1-cyclohexene and 1-chloro-2-acetylcyclohexane. Mousseron and Jacquier (156, 157) report that the addition of acetyl chloride to 1-chlorocyclopentene and 1-chlorocyclohexene also leads to mixtures of the α,β- and β,γ-unsaturated ketones.

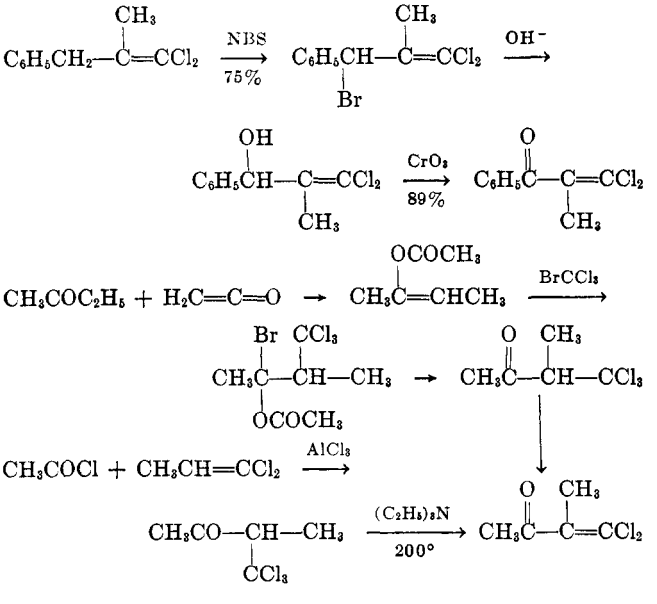


These authors also report the preparation of 1-acyl-2-chloro-1-cyclohexene by addition of alkylzinc iodides to 2-chloro-1-cyclohexene-1-carbonyl chloride.

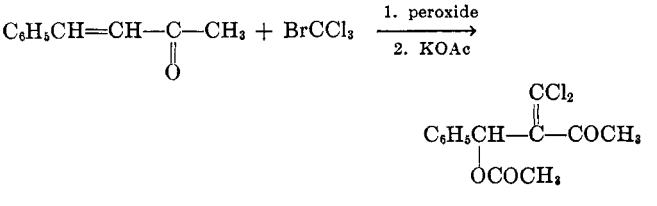


Sanchez (207) reports the preparation of certain β,β-dichlorovinyl ketones *via* Scheme XII.

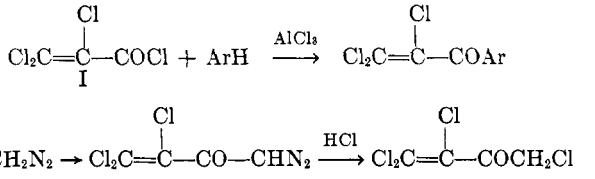
SCHEME XII



Huang (55) reports the following reaction path for his synthesis.

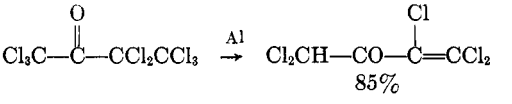


Trichlorovinyl ketones have been prepared in several ways. The most general method, however, appears to involve the Friedel–Crafts addition of trichloroacrylyl chloride to aromatic compounds in the presence of aluminum chloride (21). Alternatively, the addition of

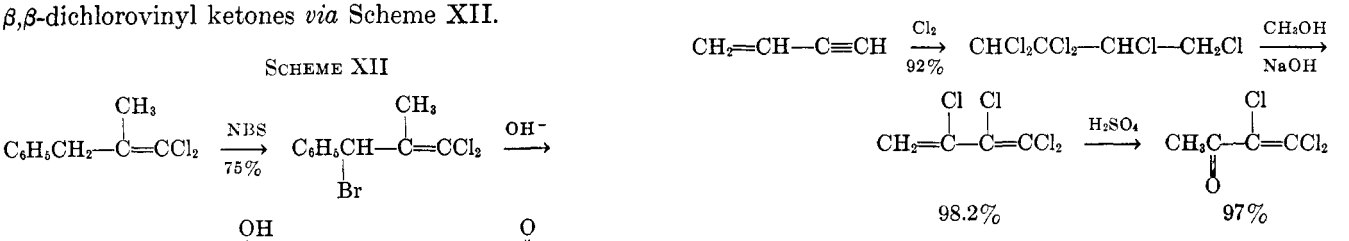


diazomethane forms the corresponding diazoketone which may then be further treated to form α,β,β-trichlorovinyl ketones (204).

Roedig and Becker (201) also found that treatment of perchlorobutanone with aluminum turnings resulted in the formation of dichloromethyl α,β,β-trichlorovinyl ketone. In a similar way, perchloro-3-pentanone yielded diperchlorovinyl ketone (58.3%).



Finally, methyl trichlorovinyl ketone was prepared (1) from vinylacetylene *via* the following reaction path.



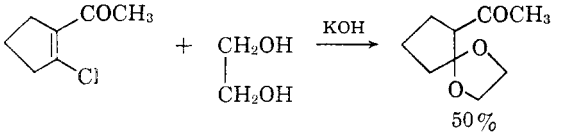
There are several reports in the literature concerning the chlorination of cyclic α-diketones leading to α-chloro α-diketones which in their enolic forms may be considered β-chlorovinyl ketones (31, 49, 50, 72, 217). Halogenated quinones are also known but will not be included in this review.

B. PHYSICAL PROPERTIES

These compounds are usually colorless oils, quite unstable in storage. The infrared and ultraviolet spectra indicate a conjugated system, but the extinction coefficients are anomalously low. Thus methyl α-methyl-β,β-dichlorovinyl ketone absorbs maximally in 95% ethanol at 245 mμ (ϵ 4600), while phenyl α-methyl-β,β-dichlorovinyl ketone absorbs at 253 mμ (ϵ 13,400). It has been suggested that in these compounds there is steric interference to coplanarity, and thus conjugation has been disrupted (207). Therefore, in these compounds the β-halogen atom is expected to be more vinylic in character, and thus nucleophilic displacement reactions should be much more difficult. The validity of this conclusion is examined next.

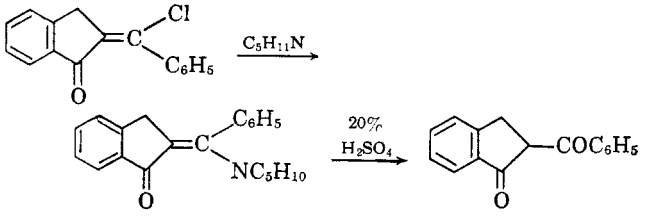
C. CHEMICAL PROPERTIES

It has been shown that in the 1-acyl-2-chloro-1-cyclopentenes, the β-chlorine atom, although far more labile than the chlorine atom of vinyl chloride, is much less reactive than that found in the β-chlorovinyl ketones discussed in sections II and IV. Thus trimethylamine forms a quaternary salt only after heating for long periods of time (128). These salts have not been isolated in pure form. With sodium iodide in acetone no reaction occurs (128). *p*-Nitrophenylhydrazine readily forms the corresponding phenylhydrazone which, however, could not be cyclized (128). Aliphatic alcohols react to give ill-defined mixtures of products. Ethylene glycol, however, does react more slowly than with β-chlorovinyl ketones of the type RCOCH=CHCl, giving the expected dioxolanes (128).

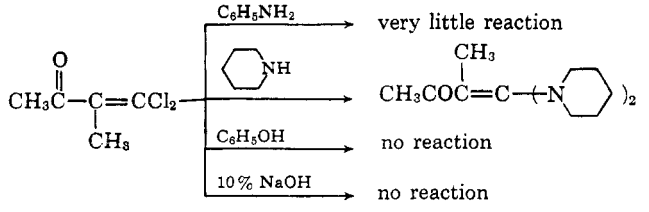


The general low reactivity of this system has been ascribed to the *cis* configuration of the chlorine atom with respect to the acyl group, to the α- and β-substitution, and to the presence of the ring (128).

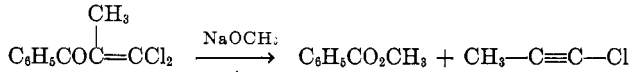
Treatment of 2-(α-chlorobenzal)-1-indanone with piperidine leads first to the formation of an unstable oil thought to be 2-(α-piperidinobenzal)-1-indanone, since on hydrolysis with 20% H_2SO_4, 2-benzoyl-1-indanone was obtained (70).



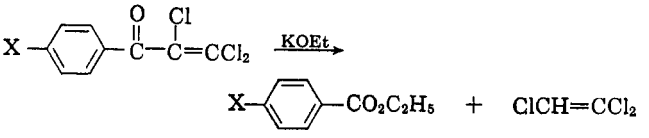
The α-alkyl-β,β-dichlorovinyl ketones have also been studied extensively. In these compounds noncoplanarity of the carbonyl and the double bond causes the β-chlorine substituents to become more vinylic and thus much more difficult to replace than those found in compounds of the type RCOCH=CCl_2 (see section IV) (207). Thus α-methyl-β,β-dichlorovinyl methyl ketone reacted very sluggishly with amines in low yields (207, 215). Under conditions analogous to those employed for the condensation of phenols with β,β-dichlorovinyl



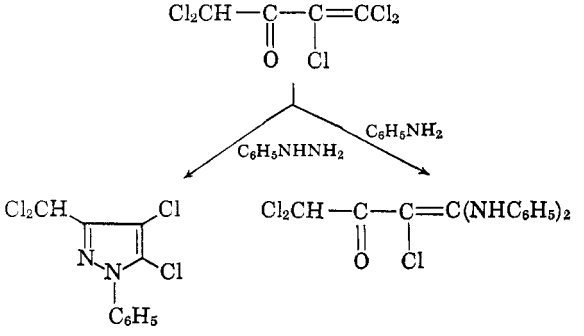
ketones of the type RCOCH=CCl_2, no reaction occurred. These compounds were virtually inert to 10% sodium hydroxide at room temperature. At 100° in 10% sodium hydroxide, the only evidence of reaction was the very slow formation of a yellow color. These compounds reacted very slowly with sodium ethoxide; however, in refluxing benzene fragmentation occurred.



In the case of trichlorovinyl ketones, fragmentation also occurs on treatment with potassium ethoxide (21, 201). However, these compounds are reported to re-



act with aromatic amines to form α-chloro-β,β-diaminovinyl ketones (199) and with phenylhydrazine to form



the corresponding pyrazole. Finally, the trichlorovinyl ketones readily add chlorine to form the corresponding pentachloroethyl ketones (21).

ACKNOWLEDGMENT.—This review was supported in part by National Institutes of Health, Neurological Diseases and Blindness, Bethesda, Md. A. E. Pohland was a Boettcher Fellow in Chemistry at Colorado State University, 1962–1963.

VI. REFERENCES

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