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The Reaction of Vinyl Chloroacetate with Some Nucleophilic Reagents

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Received August 18, 1961

The reaction of vinyl chloroacetate with a variety of nucleophilic reagents is described. With iodide, bromide, thiocyanate, diethylamine, and tertiary phosphines, vinyl chloroacetate undergoes simple nucleophilic displacement to give vinyl alpha-substituted acetates: $ClCH_2CO_2CH{=}CH_2 + X^- \rightarrow XCH_2CO_2CH{=}CH_2 + Cl^-$. Primary amines, alkoxides, and cyanides attack the carbonyl to give amides or acid salts: $ClCH_2CO_2CH{=}CH_2 + RNH_2 \rightarrow ClCH_2CONHR + CH_3CHO$. With thiosulfate and sulfite, there is concommitant displacement and hydrolysis yielding alpha-substituted acetic acid salts: $ClCH_2CO_2CH{=}CH_2 + MX \rightarrow XCH_2CO_2M + CH_3CHO$.

During the past few years vinyl chloroacetate (VCA) has received considerable attention as a component in polyesters. Relatively little attention has been devoted to the chemistry of vinyl chloroacetate, *per se*, especially nucleophilic displacements of the chlorine atom. Wiley[1] prepared vinyl dialkylphosphonatoacetates by the action of trialkylphosphites on VCA. Morrow and Ringwald[2] treated VCA with trialkylamines to obtain quaternary salts.

This paper describes the reaction of VCA with a number of nucleophilic reagents and compares ethyl chloroacetate (ECA) in several similar reactions. A semiquantitative comparison of rates of hydrolysis and displacement for VCA and ECA has also been made.

$$\underset{\text{VCA}}{ClCH_2CO_2CH{=}CH_2} \qquad \underset{\text{ECA}}{ClCH_2CO_2C_2H_5}$$

The chemical differences between VCA and ECA result from the vinyl group exerting its influence in two ways. First, the increased electronegativity of the vinyl group reduces the ability of the alkyl oxygen atom to supply electrons to the carbonyl. Thus the carbonyl is more labile to nucleophilic attack. Second, the vinyl group partially counteracts the inductive withdrawal of electrons from the alpha-carbon by the chlorine atom and makes the alpha-carbon less labile to nucleophilic attack.

A semiquantitative rate study indicates that based on reaction half-lives, ECA undergoes nucleophilic displacement by either iodide or thiocyanate ion about twice as fast as VCA. Conversely, VCA undergoes basic hydrolysis in either water or alcohol about four times as fast as ECA.

The reaction of VCA with ammonium hydroxide, alcoholic ammonia, methylamine, propylamine, and isopropylamine led in all cases to formation of the corresponding amide. Only with methylamine was there any indication of attack at the alpha carbon atom. At an 8 to 1 excess of amine over ester, a small amount of *N*-methyl methylaminoacetamide was isolated.

$$ClCH_2CO_2CH{=}CH_2 + RNH_2 \longrightarrow ClCH_2CONHR + CH_3CHO$$

ECA behaves similarly toward ammonium hydroxide,[3] alcoholic ammonia,[4] and aqueous methylamine,[5] except that with methylamine heating of the reaction mixture hydrolyzed the amide to give methylaminoacetic acid.

When VCA was treated with a series of aromatic monosubstituted amines, those which reacted gave the anilide. That the reactivity of these arylamines depended on their nucleophilicity is indicated by the sigma values of the substituents in Table I. Aniline and benzylamine replace the chlorine atom of ECA without attacking the carbonyl.[7] These reactions emphasize the differences between carbonyl and alpha-carbon reactivity of the two esters.

TABLE I

REACTION OF VCA AND AROMATIC AMINES

$ArNH_2$	Sigma[6]	Reaction
p-CH_3	−0.170	+
H	0.000	+
p-Br	+0.232	+
m-Cl	+0.373	−
p-COOEt	+0.522	−
p-NO_2	+0.778	−

VCA reacts with diethylamine to give a mixture of vinyl diethylaminoacetate and *N*,*N*-diethyl diethylaminoacetamide. The reaction of ECA with diethylamine[8] gives similar products but, as would be expected, the proportion of amide is much lower.

$$ClCH_2CO_2CH{=}CH_2 + (C_2H_5)_2NH \longrightarrow (C_2H_5)_2NCH_2CO_2CH{=}CH_2 + (C_2H_5)_2NCH_2CO_2CON(C_2H_5)_2$$

However, whereas ECA reacts readily with *N*-methylaniline,[8] VCA does not react with either *N*-methyl- or *N*-ethylaniline. The failure of VCA

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[1] R. H. Wiley, U. S. Patent **2,478,441** (1949).

[2] D. T. Morrow and E. L. Ringwald, U. S. Patent **2,653,166** (1953).

[3] E. Willm, *Ann.*, **102**, 110 (1857).

[4] W. Heintz, *Ann.*, **148**, 177 (1868).

[5] J. Volhard, *Ann.*, **123**, 261 (1862).

[6] H. H. Jaffe, *Chem. Revs.*, **53**, 191 (1953).

[7] H. Gault, *Compt. rend.*, **145**, 126 (1907).

[8] R. Willstätter, *Ber.*, **35**, 584 (1902).

to react with these amines is rather surprising on the basis of the previously mentioned 1:2 reaction factor between VCA and ECA, but probably reflects the varying rates of attack of different nucleophilic species.

The ability of VCA and ECA to quaternize[2,9] with tertiary amines suggested that a similar reaction might occur with tertiary phosphines. Treatment of VCA with tributyl- and triisobutylphosphine gave the corresponding vinoxycarbonylmethyltrialkylphosphonium chlorides. The less nucleophilic triphenylphosphine and tris-(2-cyanoethyl)phosphine did not react under the same or more vigorous conditions.

$$ClCH_2CO_2CH{=}CH_2 + R_3P \longrightarrow R_3\overset{+}{P}CH_2CO_2CH{=}CH_2{\cdot}Cl^-$$

The reactions of VCA with sodium methoxide, sodium ethoxide, and potassium phenoxide in a variety of solvents followed identical courses. In all cases, the major product was sodium or potassium chloroacetate (70–80%) and the minor product an exchange ester (15–25%)—*e.g.*, methyl chloroacetate from methoxide.

Isolation of stoichiometric quantities (based on the acid salt) of acetaldehyde and alcohol from the reaction mixture indicated that simple hydrolysis occurred; base was formed from small quantities of water present. This was confirmed by an experiment in which water was more rigorously excluded. The ratio of acid salt to ester in the products declined from 3:1 to 1:2. At no time was attack at the alpha-carbon noted.

$$ClCH_2CO_2CH{=}CH_2 + RONa \xrightarrow{HOH} ClCH_2CO_2Na + CH_3CHO + ROH$$

$$ClCH_2CO_2CH{=}CH_2 + RONa \longrightarrow ClCH_2CO_2R + (CH{=}CHONa)$$

The behavior of ECA with alkoxides again shows the striking differences between the two esters. The reaction of ECA with sodium ethoxide[10] gives a good yield of ethyl ethoxyacetate. Further, Smith[11] reported the preparation of ethyl *m*-toluoxyacetate from ECA and potassium *m*-toluoxide in ethanol which contained 10% water.

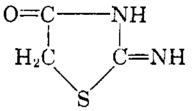
Potassium iodide, sodium thiocyanate, and potassium bromide all react readily, in the order written, with VCA in acetone to give good yields of the corresponding alpha-substituted vinyl esters. This series parallels the descending nucleophilicities of the three ions: $I^- > SCN^- > Br^-$.[12] ECA is reported to give the corresponding ethyl esters with iodide[13] and thiocyanate.[14]

$$ClCH_2CO_2CH{=}CH_2 + MX \longrightarrow XCH_2CO_2CH{=}CH_2 + MCl$$

Both thiosulfate and sulfite ion displace the chlorine of VCA. However, because of inadequate solubility of the salts in organic media, the reacactions were run under aqueous conditions where hydrolysis also occurs. Therefore, the products isolated were thiosulfato- and sulfatoacetic acid salts. ECA, on treatment with thiosulfate[15] or sulfite[16] in aqueous systems, gives the ethyl esters, another indication of the differences in lability between the two esters.

The reaction of VCA and potassium cyanide parallels the reaction of VCA and alkoxides; potassium chloroacetate is the major product. Again, this reaction can be ascribed to the presence of water and hydrolysis of the ester. ECA undergoes a normal reaction, as with alkoxides, and gives ethyl cyanoacetate.[17]

Both VCA and ECA[18] react with thiourea to give the cyclic pseudothiohydantoin (PTH). The initial point of attack, alpha-carbon or carbonyl, is uncertain as an intermediate could not be isolated even under very mild conditions.



PTH

The foregoing discussion allows certain criteria to be set up for successful displacements on the alpha-carbon of VCA. The attacking species must be highly nucleophilic and relatively soluble in nonaqueous systems. It must also be either weakly basic or a reagent which does not readily attack the carbonyl. It can be noted that all of the reagents which displaced the chlorine atom as the major reaction fulfilled both of the former conditions and at least one of the latter conditions—*e.g.*, iodide, bromide, thiocyanate, diethylamine, tertiary phosphines.

EXPERIMENTAL

Reaction of VCA and primary alkylamines. Ammonium hydroxide. VCA (2.0 g., 0.016 mole) and 20 ml. of 10% ammonium hydroxide were warmed at 50° for 5 min. VCA rapidly dissolved and, on chilling the solution, a precipitate formed. The solution was filtered and the precipitate was recrystallized from water.

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(9) H. Silberstein, *Ber.*, **17**, 2660 (1884).

(10) L. Henry, *Ber.*, **4**, 701 (1871).

(11) E. L. Smith, *J. Chem. Soc.*, 170 (1927).

(12) C. G. Swain and C. B. Scott, *J. Am. Chem. Soc.*, **75**, 141 (1953).

(13) J. B. Conant and W. R. Kirner, *J. Am. Chem. Soc.*, **46**, 249 (1924).

(14) W. Heintz, *Ann.*, **136**, 223 (1865).

(15) A. Slator, *J. Chem. Soc.*, 486 (1905).

(16) R. Andreasch, *Monats.*, **46**, 639 (1925).

(17) H. Muller, *Ann.*, **131**, 351 (1864).

(18) C. F. H. Allen and J. A. Van Allan, *Org. Syntheses*, Coll. Vol. **3**, 751 (1955).

TABLE II

REACTIONS OF VCA AND NUCLEOPHILES

Reagent	Product	M.P.	Conversion, %
NH_4OH	$ClCH_2CONH_2{}^a$	118–120	93
Alc. NH_3	$ClCH_2CONH_2{}^a$	118–119	93
CH_3NH_2 (4:1)	$ClCH_2CONHCH_3{}^a$	43–45	41
CH_3NH_2 (8:1)	$CH_3NHCH_2CONHCH_3\cdot HCl^b$	234–236	14
$C_3H_7NH_2$	$ClCH_2CONHC_3H_7{}^b$	B.p. 85–87/5 mm.	56
i-$C_3H_7NH_2$	$ClCH_2CONHC_3H_7$-i^b	60–62	60
p-$CH_3C_6H_4NH_2$	$ClCH_2CONHC_6H_4CH_3$-p^b	161–163	76
$C_6H_5NH_2$	$ClCH_2CONHC_6H_5{}^a$	136–138	63
p-$BrC_6H_4NH_2$	$ClCH_2CONHC_6H_4Br$-p^a	178–180	63
$(C_2H_5)_2NH$	$(C_2H_5)_2NCH_2CO_2CH{=}CH_2{}^c$ +	B.p. 85–87/20 mm.	20
	$(C_2H_5)_2NCH_2CON(C_2H_5)_2{}^b$	B.p. 123–125/7 mm.	16
$(C_4H_9)_3P$	$(C_4H_9)_3\overset{+}{P}CH_2CO_2CH{=}CH_2\cdot Cl^{-d}$	95–97	66
$(i$-$C_4H_9)_3P$	$(i$-$C_4H_9)_3\overset{+}{P}CH_2CO_2CH{=}CH_2\cdot Cl^{-e}$	93–95	44
CH_3ONa	$ClCH_2CO_2Na^a$ +	180–185 dec.	74
	$ClCH_2CO_2CH_3{}^a$	B.p. 63–65/100 mm.	17
CH_3ONa (anhyd.)	$ClCH_2CO_2Na^a$ +	180–185 dec.	16
	$ClCH_2CO_2CH_3{}^a$	B.p. 72–74/150 mm.	31
C_2H_5ONa	$ClCH_2CO_2Na^a$ +	180–185 dec.	67
	$ClCH_2CO_2C_2H_5{}^a$	B.p. 80–83/100 mm.	23
C_6H_5OK	$ClCH_2CO_2K^a$ +	155–160 dec.	71
	$ClCH_2CO_2C_6H_5{}^b$	B.p. 106–109/23 mm.	19
KBr	$BrCH_2CO_2CH{=}CH_2{}^a$	B.p. 51–54/10 mm.	61
KI	$ICH_2CO_2CH{=}CH_2{}^b$	B.p. 58–60/4 mm.	46
KSCN	$NCSCH_2CO_2CH{=}CH_2{}^f$	B.p. 91–92/1.5 mm.	61
$Na_2S_2O_3$	$NaO_3S_2CH_2CO_2Na^a$	200–250 dec.	35
K_2SO_3	$KO_3SCH_2CO_2K^a$	200–250 dec.	43
KCN	$ClCH_2CO_2K^a$	155–160 dec.	75
$(NH_2)_2C{=}S$	$C_3H_4N_2OS^a$	235–246 dec.	76

[a] Identified by comparison with authentic sample. [b] Identified by infrared and physical constants. [c] Calcd.: C, 61.1; H, 9.5; N, 8.9. Found: C, 61.5; H, 9.4; N, 9.4. [d] Calcd.: C, 59.5; H, 9.9; Cl, 11.0. Found: C, 59.1; H, 10.1; Cl, 11.7. [e] Calcd.: C, 59.5; H, 9.9; Cl, 11.0. Found: C, 59.2; H, 10.1; Cl, 11.6. [f] Calcd.: C, 42.0; H, 3.5; N, 9.8. Found: C, 42.4; H, 4.0; N, 9.8.

Alcoholic ammonia. A solution of VCA (2.0 g., 0.016 mole) in 50 ml. of absolute ethanol was cooled to 5° and dry ammonia gas was bubbled through. A precipitate rapidly formed. The precipitate was filtered and recrystallized from water.

Methylamine in 4 to 1 excess. VCA (2.0 g., 0.016 mole) was slowly added to 40 ml. of 5% aqueous methylamine cooled in an ice-bath. VCA slowly dissolved and, on standing, a yellow precipitate formed. The precipitate was filtered, washed with ether and dried over phosphorus pentoxide.

Methylamine in 8:1 excess. The above experiment was repeated using 10 ml. of 40% aqueous methylamine. The solution was allowed to stand overnight and the solvent was evaporated. The residue, a viscous oil, partially crystallized on standing several days. The solid portion was separated and recrystallized from ethanol-water.

Propylamine. VCA (2.0 g., 0.016 mole) was slowly added to propylamine (4.7 g., 0.080 mole) chilled in an ice bath. After 4 hr., excess amine was distilled and the product was cbtained by distillation at reduced pressure.

Isopropylamine. The above experiment was repeated using isopropylamine. The excess amine was evaporated and the residue distilled to give a colorless oil which solidified on standing.

Reaction of VCA and aromatic amines. General method. VCA (2.0 g., 0.016 mole) and the aromatic amine (0.032–0.035 mole) in 30 ml. of benzene were refluxed for 3 hr. The solution was cooled and the precipitate was recrystallized from ethanol-water.

Vinyl diethylaminoacetate. VCA (12 g., 0.10 mole) was slowly added to diethylamine (14.6 g., 0.20 mole) at −5°. A precipitate rapidly formed and the solution turned darkred. After 4 hr. at −5°, the mixture was allowed to stand overnight at room temperature. The semisolid mass was triturated with 100 ml. of benzene, filtered, and the benzene was distilled. The residue was then fractionated at reduced pressure.

Vinoxycarbonylmethyltributylphosphonium chloride. A solution of tributylphosphine (20 g., 0.10 mole) in 50 ml. of benzene was slowly added to an ice-cooled solution of VCA (12 g., 0.10 mole) in 50 ml. of benzene under nitrogen. After 2 hr., the precipitate was filtered and recrystallized from benzene.

Vinoxycarbonylmethyltriisobutylphosphonium chloride. A solution of VCA (12 g., 0.10 mole) and triisobutylphosphine (20 g., 0.10 mole) in 60 ml. of benzene was warmed to 35° when a precipitate began to form. The mixture was then chilled for 2 hr. The precipitate was filtered and recrystallized from benzene.

Reaction of VCA and alkoxides. Sodium methoxide. VCA (120 g., 1.0 mole) was slowly added to an ice-cooled slurry of sodium methoxide (54 g., 1.0 mole) in 500 ml. of xylene. The mixture was held at 5° for 3 hr., then allowed to stand

3 hr. at room temperature. The solution was filtered and the solid was washed with ether and dried to give 74% of sodium chloroacetate. Evaporation of the ether washings gave 5.9 g. of acetaldehyde-aldol-crotonaldehyde polymer. The filtrate was fractionated on a Todd column and the fractions treated with 2,4-dinitrophenylhydrazine to obtain (as 2,4-dinitrophenylhydrazones): acetaldehyde (6.5 g.), aldol (14.8 g.), and crotonaldehyde (3.0 g.). The combined yield of acetaldehyde was 68%. The fractionation also gave methyl chloroacetate (17% based on VCA) and methanol (66%).

Sodium ethoxide and potassium phenoxide. Repeats of the above experiment using sodium ethoxide in absolute ethanol and potassium phenoxide in absolute methanol gave similar results. (See Table II for yields.)

Vinyl bromo (iodo-, thiocyanato)acetate. A mixture of VCA (12 g., 0.10 mole), the corresponding salt (0.10 mole) and 100 ml. of acetone was treated as follows: Potassium bromide: refluxed 3 hr.; Potassium iodide: stirred 3 hr. at room temperature; Sodium thiocyanate: warmed 2 hr. at 60°. The mixture was poured into 300 ml. of water. The salts dissolved and two layers formed. The organic layer was separated, dried over calcium sulfate, and the acetone was distilled. Distillation of the residue at reduced pressure gave the vinyl ester.

Reaction of VCA with sodium thiosulfate and potassium sulfite. VCA (12 g., 0.10 mole), the salt (0.10 mole), 60 ml. of ethanol, and 40 ml. of water were refluxed for 2 hr. The solution volume was reduced to 20 ml. by distillation and the residue was allowed to stand 72 hr. at room temperature. The precipitate was filtered and extracted with 5 × 200 ml. of cold, absolute methanol. Evaporation of the methanol gave the acid salt.

Reaction of VCA and potassium cyanide. VCA (24 g., 0.20 mole), potassium cyanide (14 g., 0.22 mole), and 200 ml. of absolute ethanol were mixed and placed under a reflux condenser. Considerable heat was evolved and the mixture turned dark red. After the exotherm had subsided, the mixture was refluxed for 2 hr., cooled, and filtered. The solid was washed with ether and dried.

Reaction of VCA and thiourea. VCA (12 g., 0.10 mole) was added to a stirred mixture of thiourea (7.6 g., 0.10 mole) and 100 ml. of acetone. The mixture was refluxed 1 hr., cooled, and filtered. The precipitate was treated with 300 ml. of water in which most of it dissolved. The aqueous solution was filtered and treated with saturated, aqueous sodium carbonate until neutral to litmus. On chilling, a crystalline precipitate formed.

Comparative rates of displacement of VCA and ECA. VCA (2.40 g., 0.020 mole) was added to potassium iodide or sodium thiocyanate (0.020 mole) in 25 ml. of acetone at 25 ±2°. Samples were periodically withdrawn and the reaction followed by the decrease in the area of the band for VCA on a vapor phase chromatograph.[19] The time required for the concentration of VCA to fall to one-half its original value ($t_{1/2}$) was 7.5 min. (to the nearest 0.5 min.) for iodide and 96 minutes (to the nearest 1 min.) for thiocyanate. ECA, under the same conditions, gave corresponding values of 4.0 min. and 51 min.

Comparative rates of hydrolysis of VCA and ECA. VCA (1.20 g., 0.10 mole) was stirred with 50 ml. of 1.086 N sodium hydroxide at 25 ±2°. Aliquots of 1 ml. were periodically withdrawn and titrated to a phenolphthalein end-point with 0.970 N hydrochloric acid. The $t_{1/2}$ of the reaction was 2.5 min. The comparable value for ECA was 10.0 min.

A similar study in alcoholic sodium hydroxide (0.150 N) which was followed by vapor phase chromatography gave a value of 3.5 min. for $t_{1/2}$ for VCA and 11.5 min. for ECA.

Acknowledgment. The author is indebted to Mr. N. Colthup for analysis of infrared spectra and to the Microanalytical Group, Research Service Department, Stamford Research Laboratories, for microanalyses.

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[19] "Aerograph" Wilkens Instrument and Research, Inc., Walnut Creek, Calif.