I. SYNTHETIC STUDIES ON TERTIARY VINYLOGOUS AMIDES AND RELATED COMPOUNDS

II. COBALT(II) CHLORIDE COMPLEXES OF TERTIARY VINYLOGOUS AMIDES AND RELATED LIGANDS

Thesis by
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"One hour in the library is worth one week at the bench."

--J. B. Ellern

"You can miss a lot of interesting chemistry that way."

--R. E. Ireland rejoinder to above

"A sufficiently naive reader might get the impression that no experiments have ever been done...he might even conclude that there is no need to do any, since whatever is of importance can be predicted *a priori*. It is, of course, typical of physical theory to stand as a proud and arrogant edifice, pretending that it could have been constructed without the much less elegant scaffolding of experimental observation."

--Gabriel Weinreich, in preface to "Solids:
Elementary Theory for Advanced Students," 1965.

"And still during their brief appearance on earth, men convince themselves that they leave behind some trace... yes, even a fly casts a shadow."

--Chateaubriand, "Memoirs from Beyond the
Grave"

ACKNOWLEDGMENTS

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I acknowledge helpful discussions with Drs. Robert Ireland, Robert Bergman, John Bercaw, and Joseph Gordon. The assistance of Susan Brittenham throughout my graduate study and in typing this thesis has been invaluable.

I am grateful to the National Science Foundation and to Caltech for support during these studies.

The friendship and hospitality of my "Los Angeles Family," the Robert Mendelsons, is gratefully acknowledged. The love of Lynn and Ann Bailey has nourished my soul, especially when it was very hungry. Kay Hooley has provided much needed moral support over the last few months during the writing of this thesis.

ABSTRACT

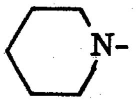
Tertiary vinylogous amides, both open-chain and cyclic, were prepared by several routes with a view toward their use as ligands for metal ions. It is shown that the thermodynamically preferred isomer (functionality trans) is the exclusive product in the open chain case. A new convenient synthesis of β-aminobutenones is described.

In contrast to previous studies, it was found that activated vinylidene chlorides (AVDC's) with α-hydrogen ($Cl_2C{=}CH{-}L$, L = carbonyl function or cyano), react with certain secondary amines to give acetylenes, $R_2N{-}C{\equiv}C{-}L$, either as intermediates or final products except with L = CHO. The mechanism of this reaction is discussed. A simple synthesis of 3,3-dichloropropenoic acid and its conversion to several functional derivatives are described. A case is presented for rotational isomerism in four β,β-dichlorovinyl carbonyl compounds.

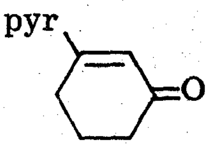
Nuclear magnetic resonance and infrared spectral correlations were made for the compounds prepared. In particular, it is shown that nmr spectroscopy allows ready distinction of piperidino vinylogous ureas from the isomeric acyl ketenaminals of this amine.

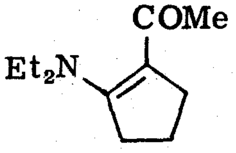
Synthesis and partial characterization of complexes of some of the above polarized ethylenes and acetylenes with cobalt(II) chloride are reported. The polarized ethylenes behave somewhat like tertiary amides as ligands; in two cases, different forms of complex with same ligand were found. The "push-pull" acetylenes form 1:1 complexes in which the triple bond absorption(s) of the ligand is absent. The possible implications of this result are discussed.

KEY TO ABBREVIATIONS
FOR PARTS I and II

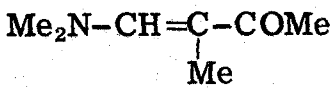
AVDC	activated vinylidene chloride, $Cl_2C-\overset{|}{C}-L$ (L = carbonyl function or CN).
DCE	$ClCH_2CH_2Cl$
pip	
pyr	
DMP	$Me-C(OMe)_2-Me$

KEY TO NUMBERED COMPOUNDS FOR PARTS I and II

1 

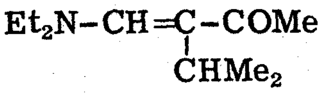
2 

3 $Me_2N-CH=CH-COMe$

4a 
$Me_2N-CH=\underset{Me}{C}-COMe$

4b $Me_2N-CH=CH-COEt$

5 $Et_2N-CH=CH-CHMe_2$

6a 
$Et_2N-CH=\underset{CHMe_2}{C}-COMe$

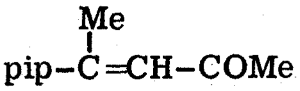
6b $Et_2N-CH=CH-COCH_2CHMe_2$

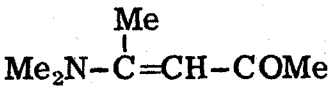
7 $(MeO)_2CH-CH_2COMe$

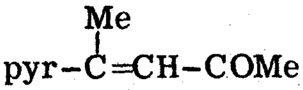
8 MeO–CH=CH–COMe

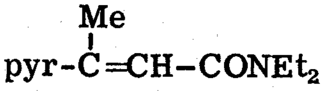
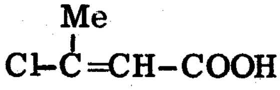
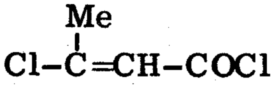
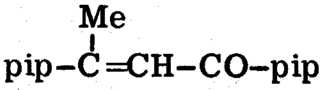
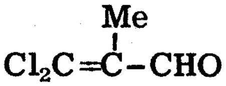
9 $\underline{t}$–Bu–NH–CH =CH–COMe

10 $MeCOCH_2COMe$

11 
$pip-\overset{Me}{C}=CH-COMe$

12 
$Me_2N-\overset{Me}{C}=CH-COMe$

13 
$pyr-\overset{Me}{C}=CH-COMe$

14	$\mathrm{pyr{-}CH{=}CH{-}COMe}$
15	 $\mathrm{pyr{-}\overset{\overset{Me}{\vert}}{C}{=}CH{-}CONEt_2}$
16	$\mathrm{pip{-}CH{=}CH{-}CO{-}pip}$
17	*cis* and *trans*  $\mathrm{Cl{-}\overset{\overset{Me}{\vert}}{C}{=}CH{-}COOH}$
18	*cis* and *trans*  $\mathrm{Cl{-}\overset{\overset{Me}{\vert}}{C}{=}CH{-}COCl}$
19	 $\mathrm{pip{-}\overset{\overset{Me}{\vert}}{C}{=}CH{-}CO{-}pip}$
20	$\mathrm{Cl_2C{=}CH{-}COMe}$
21a	$\mathrm{Cl_2C{=}CH{-}COPh}$
21b	$\mathrm{Cl_3C{-}CH_2{-}COPh}$
22a	$\mathrm{Cl_2C{=}CH{-}COCH_2Cl}$
22b	$\mathrm{Cl_3C{-}CH_2{-}COCH_2Cl}$
23	$\mathrm{Cl_2C{=}CH{-}COCHMe_2}$
24	$\mathrm{Cl_2C{=}CH_2}$
25	$\mathrm{Cl_2C{=}CH{-}CHO}$
26	 $\mathrm{Cl_2C{=}\overset{\overset{Me}{\vert}}{C}{-}CHO}$
27	$\mathrm{Cl_2C{=}CH{-}COOH}$
28	$\mathrm{Cl_2C{=}CH{-}COCl}$
29	$\mathrm{Cl_2C{=}CH{-}COOMe}$
30	$\mathrm{Cl_2C{=}CH{-}CONH_2}$
31	$\mathrm{Cl_2C{=}CH{-}CN}$

32	$\mathrm{Et_2N{-}C{\equiv}C{-}COMe}$
33	$\mathrm{(pip)_2C{=}CH{-}COMe}$
34	$\mathrm{(Me_2N)_2C{=}CH{-}COMe}$
35	$\mathrm{Cl_2C{=}CH{-}CO{-}N(CHMe_2)_2}$
36	$\mathrm{(Me_2CH)_2N{-}C{\equiv}C{-}CN}$
37	$\mathrm{CoCl_2}$

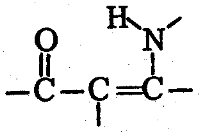
(An expanded key to species 38-45 is Table II, Part II.)

38	$\mathrm{CoCl_2 \cdot 2\ (1)}$
39	$\mathrm{CoCl_2 \cdot x\ (2)}$
40	$\mathrm{CoCl_2 \cdot 2\ (3)}$
41	$\mathrm{CoCl_2 \cdot 2\ (13)}$
42	$\mathrm{CoCl_2 \cdot x\ (16)}$
43	$\mathrm{CoCl_2 \cdot 2\ (33)}$
44	$\mathrm{CoCl_2 \cdot (32)}$
45	$\mathrm{CoCl_2 \cdot (36)}$

TABLE OF CONTENTS

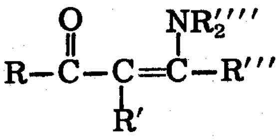
GENERAL INTRODUCTION TO PARTS I AND II

Several years ago, I decided to undertake the study of transition metal complexes of β-dialkylamino-α,β-enones. Such ligands (more accurately <u>possible</u> ligands) are related to two groups of compounds whose complexes have been extensively studied: (1) β-dicarbonyl compounds and their nitrogen analogs,



$-\overset{\overset{O}{\|}}{C}-\underset{|}{C}=\overset{\overset{H\diagdown N\diagup}{|}}{C}-$,[1] and tertiary amides.

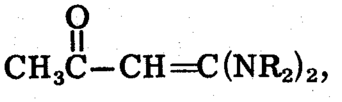
The relationship to the first group lies in the fact that the compounds



$R-\overset{\overset{O}{\|}}{C}-\underset{\underset{R'}{|}}{C}=\overset{\overset{NR_2''''}{|}}{C}-R'''$ can at least possibly bind to a metal simultaneously through both the N and the O, or even at α-C (as do mercury and platinum to acetylacetone[2]). A crucial difference is the absence of an acidic hydrogen in my compounds; the complexes of enamino ketones previously studied have been those of the mono-anion. Thus, my compounds are enamino (or ynamino) carbonyl compounds "locked" in this tautomeric form.

Secondly, my compounds are vinylogs* of tertiary carboxamides. Their organic chemistry reflects this fact; they fail to give normal ketone and aldehyde derivatives such as phenyhydrazones, have amidic carbonyl stretching frequencies,[3] and hydrolyze to vinylogous acids or their reaction products.[4] The cobalt(II) coordination chemistry of these compounds (Part II of this thesis) reflects the amidic character of these ligands in some cases.

Vinylogs generally can have both a more variable stereochemistry and functionality than the simple compounds to which they are related. The latter aspect led to a discovery which is a major part of Part I, a brief history of which is as follows:

In an attempt to prepare  $CH_3\overset{O}{\overset{\|}{C}}-CH=C(NR_2)_2$, 4,4-dichloro-3-buten-2-one was reacted with diethylamine in ether. The surprising result (to me at least) was nearly exclusive formation of the ethynylogous amide ("push-pull" acetylene[6]), 4-diethylamino-3-butyn-2-one.

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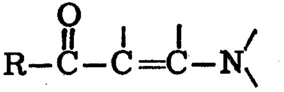
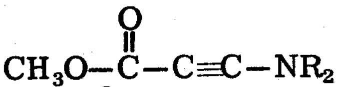
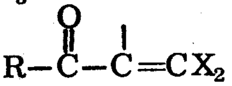
*Vinylog will be used to refer to compounds in which two pieces of a polyatomic functional group are attached by a carbon-carbon double bond; thus  $R-\overset{O}{\overset{\|}{C}}-\overset{|}{C}=\overset{|}{C}-N\langle$ is a vinylogous carboxamide. A compound A—C≡C—B is an ethynylog of A—B[5];  $CH_3O-\overset{O}{\overset{\|}{C}}-C\equiv C-NR_2$ is an ethynylogous urethane. Compounds such as  $R-\overset{O}{\overset{\|}{C}}-\overset{|}{C}=CX_2$ will sometimes be called vinylidenologs of  $R-\overset{O}{\overset{\|}{C}}-X$ (nomenclature original). Vinylog will occasionally be used in a broad sense to refer to all the above classes of compounds.

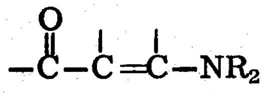
This discovery was followed by an extensive investigation of syntheses and reactions of activated vinylidene chlorides, X—CH=CCl_2 (X = carbonyl function or –CN), mostly with amines.

The original impetus for all these studies was to prepare and characterize complexes of the ligands. I had discovered early in my graduate work that simple open chain vinylogous amides dissolve cobalt(II) chloride to give complexes soluble in polar chlorinated solvents. These complexes and those of other potential ligands prepared during the organic phase were then investigated. These studies constitute Part II of this thesis.

PART I

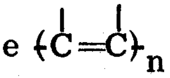
SYNTHETIC STUDIES ON TERTIARY VINYLOGOUS AMIDES AND RELATED COMPOUNDS

CHAPTER I

Simple Vinylogous Carboxamides, Functionality  $-\overset{\overset{O}{\|}}{C}-\overset{|}{C}=\overset{|}{C}-NR_2$

The Vinylogy Principle

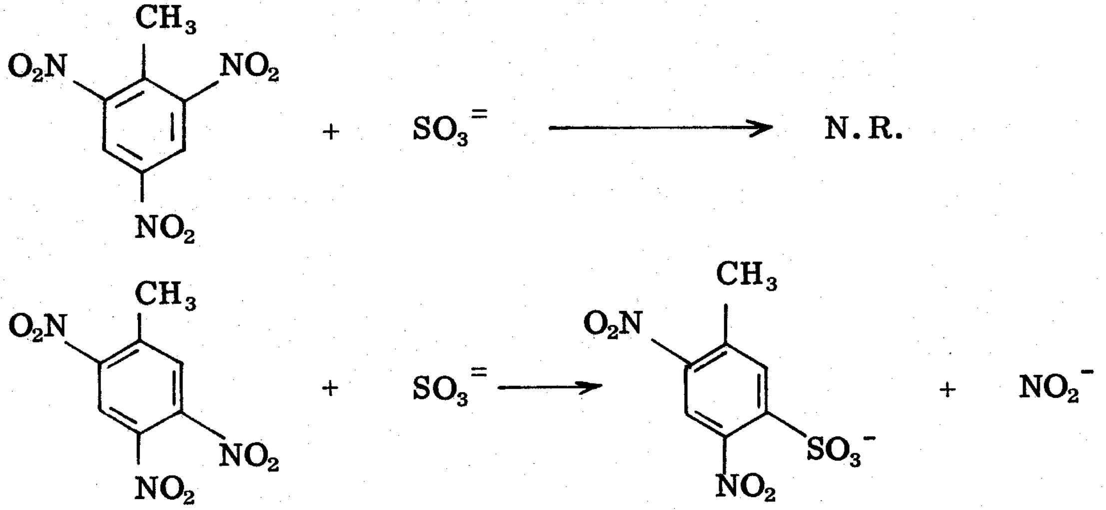
The vinylogy principle is fundamental to the bulk of the work described in this thesis. Accordingly, the historical development and a somewhat extended discussion of this concept is set forth in this section.

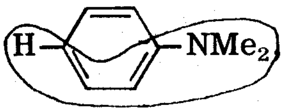
"It has long been recognized that in a molecule containing a system of conjugated double linkages, the influence of a functional group may sometimes be propagated along the chain and make itself apparent at a remote point in the molecule." Thus begins the 1935 review by Fuson[7] of the same title as this section. His article treats in an empirical and correlative way a large number of observations on the courses of certain reactions, all of which can be summarized in his definition of vinylogy: "When in a compound of the type $A-E_1=E_2$ or $A-E_1\equiv E_2$, a structural unit of the type  $(\overset{|}{C}=\overset{|}{C})_n$ is interposed between A and E_1, the function of E_2 remains qualitatively unchanged but that of E_1 may be usurped by carbon atom attached to A." Following this definition, Fuson would say in regard to the participation of crotonic esters, $CH_3-CH=CH-COOR$ in aldol condensations, that the role of the carbonyl carbon in labilizing α-hydrogens to removal by bases in acetic esters is "usurped" by the β-vinyl carbon in crotonates.

An alternate definition of vinylogy which focuses more on the two piece nature of many reactive units is given by Blatt[8]: "... when a given effect on the reactivity of a functional group is produced by a saturated substituent attached directly to that functional group, a similar effect may be produced by the same substituent when it is separated from the functional group by an intervening vinylene group." In more graphic language, this amounts to saying that when X is a saturated substituent and Y is some functional group, $X\left(\overset{|}{C}=\overset{|}{C}\right)_n Y$ may behave like X—Y.

Well-known reactions exemplary of the vinylogy principle are the conjugate addition to α,β-unsaturated carbonyl compounds of Grignard reagents, amines, and of the anions of active methylene compounds (Michael reaction). The transmittal of vinylogous activation through several vinylene groups is illustrated by the condensation of diethyl oxalate with $CH_3(CH{=}CH)_4COOEt$ to give $HOOC(CH{=}CH)_5COOH$.[9] This phenomenon is also responsible for the fact that mild conditions are required to obtain good yields of aldol,[9] $CH_3{-}CH(OH){-}CH_2{-}CHO$ from acetaldehyde; with strong base, aldol is dehydrated to crotonaldehyde, which condenses with more acetaldehyde or with itself.[9]

A system may also show vinylogous behavior where the vinyl group(s) connecting two parts of a reactive unit is part of an aromatic ring. A classic example is the nitrotoluenes. The ortho and para compounds undergo Claisen-Schmidt type condensations since they contain the groupings $CH_3{-}CH{=}CH{-}NO_2$ or $CH_3(CH{=}CH)_2NO_2$ and are therefore vinylogs of nitromethane. The meta compound does not give an analogous reaction.[7,9] Similarly, leaving groups *ortho* and/or *para* to aromatic nitro groups are labilized toward nucleophilic substitution; 2,4-dinitrochlorobenzene reacts readily with amines to give 2,4-dinitroanilines. Aromatic nitro groups even labilize other *ortho* or *para* nitro groups. This fact has been of commercial importance in the purification of the valuable explosive, 2,4,6-trinitotoluene (TNT). Heating TNT contaminated with other trinitrotoluenes with aqueous sodium sulfite removes the latter as water-soluble sulfonic acids[10] since they all have at least one nitro group *ortho* and/or *para* to another, which is therefore activated toward substitution:

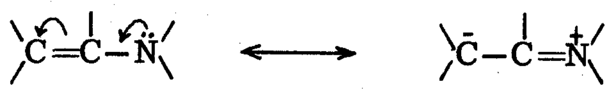


A final classic reaction illustrating vinylogous activation through an aromatic ring is the reaction of phosgene and N,N-dimethylaniline *without* a catalyst to give *p*,*p*'-dimethylaminobenzophenone (Micheler's ketone). For this reaction, N,N-dimethylaniline can be regarded as a vinylog of a *secondary* amine,  which reacts with

$COCl_2$ to yield the vinylogous urea, Micheler's ketone.

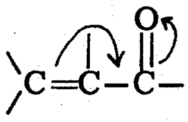
The last example serves to introduce the major relatively recent exploitation of the vinylogy concept, viz. the development of the use of aliphatic enamines, $-\overset{|}{C}=\overset{|}{C}-NR_2$, in synthesis, begun by Stork's group in the mid-1950's.[12a,b] The development of enamine chemistry through 1968 is well covered in a recent compedium of eight articles.[13] Specific relevant aspects of this chemistry will be discussed in subsequent sections.

A brief exposé of the electronic theory of vinylogy is appropriate at this point. The early workers cited above paid no or very little attention to any unifying theoretical basis for vinylogous reactivity. The word "electron" occurs nowhere in Fuson's review,[7] and Whitmore's text[9] treats theory rather gingerly. However, excellent although scattered treatment is given in the recent text by Hendrickson, Cram, and Hammond.[14] A fair summary of the electronic basis of vinylogy is that a vinylene group acts as a conduit for the transfer of electron density to or from the atom on the α-vinyl carbon to or from the β-vinyl carbon. Thus, for enamines, the β-vinyl carbon acquires electron density from the nitrogen:

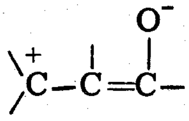


Ia **Ib**

For α,β-unsaturated carbonyl compounds, the β-carbon loses electron density to the carbonyl carbon:



IIa

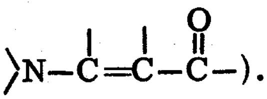


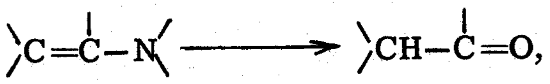
IIb

In resonance language, one says that the right-hand structures are important contributions to the electronic state of the molecule. In molecular orbital language, one eschews curved arrows and (formally) moving electrons and says that in Ia the unshared pair on nitrogen interacts with the carbon-carbon double bond in such a way that there is a partial negative charge on the β-carbon; for IIa, one says that the two double bonds interact such that both of their orders are lowered and that the molecule is partially polarized in the sense of IIb. The *physical* experimental manifestations of the theory are, e.g., for enamines the high field chemical shift of β-vinyl protons (3.5-5.0 δ)[15] more like that of an amine than a simple olefin (5-8 δ).[16] For compounds like II, one observes that both double bond stretching frequencies are lower than in non-conjugated compounds.[16,17]

Throughout my work, I have found the vinylogy concept and the associated electronic theory a most useful way of understanding the systems with which I have worked. This principle will be constantly invoked in this thesis with respect to both the physical properties (especially spectra) and the chemical reactivity of the compounds discussed.

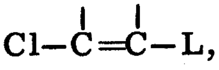
Stereochemistry

Organic *synthetic* chemists have usually been little concerned about the stereochemical disposition of groups about the olefinic bond in vinylogous amides ( $>N-\overset{|}{C}=\overset{|}{C}-\overset{\overset{O}{\|}}{C}-$). Two reasons for this are: (1) if the olefinic bond is in a ring of seven or fewer members, the stereochemistry is pre-determined; and/or (2) the worker usually intends to hydrolyze the enamine part to a carbonyl group eventually,

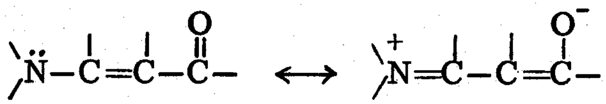


$$>C=\overset{|}{C}-N< \longrightarrow >CH-\overset{|}{C}=O,$$

in which case the stereochemistry of the intermediate is unimportant.

However, for my intended purpose, viz. the use of tertiary vinylogous amides as ligands for a metal, I deemed knowledge of the stereochemistry as of great importance since only a compound with the amine and carbonyl function *cis* could possibly chelate. In this connection, organic *mechanistic* chemists have agonized at length over two apparently conflicting pieces of data: (1) nucleophilic substitution on vinylogous acid chlorides,  $Cl-\overset{|}{C}=\overset{|}{C}-L$,(L = carbonyl function, CN, SO_2R), generally proceeds with retention of configuration; and (2) with ordinary secondary amines, only one isomeric product is obtained from either *cis* or *trans* substrates.[18] By 1970, with Truce and Gorbaty's showing that azirdine *does react with retention* with the above vinyl halides, it could be concluded that *in vinylogous amides in which the nitrogen can readily become trigonal, the barrier to rotation about the formally olefinic bond is low enough that the thermo-*

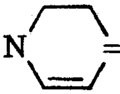
dynamically stable isomer is obtained at room temperature, i.e., that the zwitterionic structure



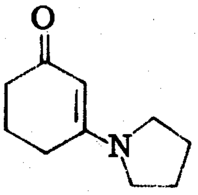
$$\rangle\ddot{N}-\overset{|}{C}=\overset{|}{C}-\overset{O}{\overset{\|}{C}}- \longleftrightarrow \rangle\overset{+}{N}=\overset{|}{C}-\overset{|}{C}=\overset{O^-}{\overset{|}{C}}-$$

is important in the ground state. The stable structure characterically has the functionality *trans*.[18] In some compounds the rotation barrier about the C—N bond is greater than that about the formally olefinic bond.[19, 20]

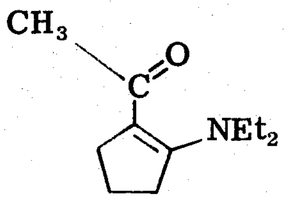
When the nitrogen is primary or secondary, both *cis* and *trans* enamine isomers can be observed by nmr and sometimes isolated. Their interconversion is measurably slow because each is stabilized by either intramolecular (*cis*) or intermolecular (*trans*) hydrogen bonding.[21] For these compounds, isomerization could occur through the tautomeric imine-ketone form, but that it does not do so exclusively is shown by the fact that isomerization is faster than deuterium exchange.[22]

It should also be mentioned that for a vinylogous amide to be even a possibly chelating ligand, not only must the amine and carbonyl functions be *cis*, but the carbonyl and olefin moities must be able to be *s*-*cis*. Compounds like γ-pyridones and their 2,3-dihydro derivatives, —N=O, are constrained to be *cis* but also *s*-*trans*. Such compounds were not studied.

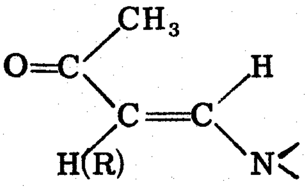
The following types of simple tertiary vinylogous amides were studied in this work*:



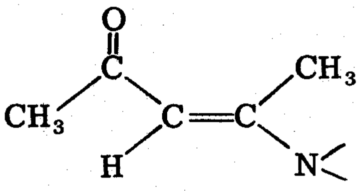
Type I
locked *trans*
locked *s*-*trans*



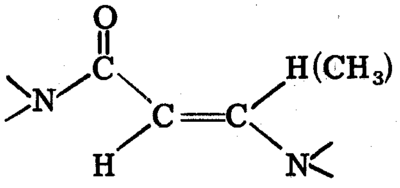
Type II
locked *cis*
s-*cis*



Type III
mobile *trans*
s-*cis*, *s*-*trans*



Type IV
mobile *trans*
s-*cis*



Type V
mobile *trans*?
s-*cis*?

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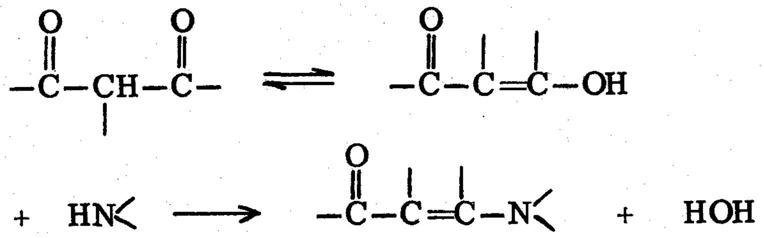
*A "simple vinylogous amide" is one which has *one* amine group and *one* carbonyl function on opposite ends of a vinyl group. For variety of expression, vinylogous amides generally will sometimes be called "push-pull" or "polarized" ethylenes or olefins. Unless otherwise noted, *cis* and *trans* refer to the disposition of the amine and carbonyl functions about the vinyl linkage.

For Type I, the assertions about configuration are obvious. That types II and IV are s-cis follows from the studies showing that with a group even as large as methyl cis to an acetyl group, the s-cis conformation is predominant or even exclusive; the s-trans conformation is disfavored by its inability to be planar.[23a, b, c] For Types IV and V (β-H) the trans configuration is established by the coupling constant of the vinyl protons (J ~ 13 Hz, a typical trans value,[18] versus J = 8 for the cis-locked N-methyl-2, 3-dihydro-4-pyridone[24]). Tertiary β-amino butenones show s-cis, s-trans isomerism on the IR time scale.[23a] The word "mobile" follows from the previous discussion about the facile isomerism of "push-pull" olefins. The trans configuration for Type IV has been assigned on a variety of spectral grounds[18]; for the vinylogous area Type V with β-methyl, no configuration assignment has been made. My evidence confirming the trans configuration for Type IV and suggestive thereof for Type V will be set forth below. The steric relationship of the carbonyl and ethylene linkages in the Type V compounds is not known; certainly the s-cis conformation is accessible.

Syntheses--Evaluation of Approaches

With the vinylogy principle in mind, several synthetic approaches to the preparation of vinylogous suggest themselves:

(1) Reaction of a vinylogous acid (β-dicarbonyl compound) or its salt with an amine or its salt under dehydrating conditions.



$$-\overset{O}{\overset{\|}{C}}-\underset{|}{CH}-\overset{O}{\overset{\|}{C}}- \rightleftharpoons -\overset{O}{\overset{\|}{C}}-\overset{|}{C}=\overset{|}{C}-OH$$

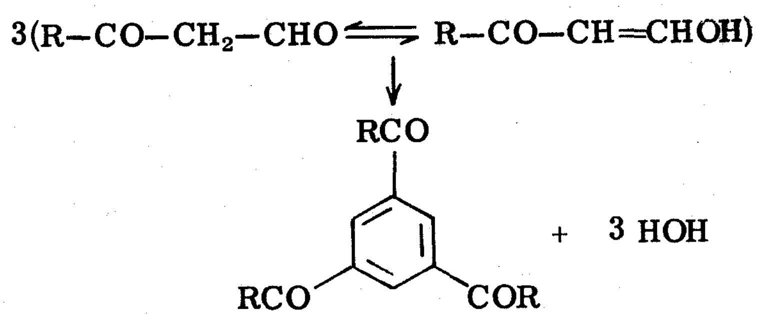
$$+\ HN\langle \longrightarrow -\overset{O}{\overset{\|}{C}}-\overset{|}{C}=\overset{|}{C}-N\langle \ +\ HOH$$

(2) Reaction of a vinylogous acid chloride (β-chlorovinyl carbonyl compound) or vinylogous ester (β-alkoxyvinyl carbonyl compound) with an amine.

(3) Addition of an amine to an α,β-acetylenic carbonyl compound.

(4) Acylation of a vinylogous amine(enamine).

Method (1) is the original way in which a number of β-enamino ketones ("β-acylvinylamines"), $R{-}CO{-}\overset{|}{C}{=}CH{-}N\langle$, were made in unstated yield.[25] With some amines this method gives completely or in part substituted pyridines which are hard to separate from the desired compound.[1b, 25] The starting β-ketoaldehydes/hydroxymethyleneketones are prepared by Claisen condensation of a ketone with a formic ester.[26] β-ketoaldehydes unsubstituted at the central methylene must be used as the salt with the amine salt; attempts to obtain the free aldehyde give 1,3,5-acylbenzenes[27, 28]:



When the central methylene is mono- or disubstituted, the free aldehyde is stable.[4, 25, 29, 30, 31]

The direct reaction of a β-dicarbonyl compound and an amine (Method (1)) has also been used to obtain enamino ketones derived from 1, 3-cyclohexanedione(dihydroresorcinol)[32] and acetylacetone.[33-37] The ease with which secondary amines yield the desired product with acetylacetone is very sensitive to hindrance in the amine. Pyrrolidine gives 4-N-pyrrolidino-3-penten-2-one readily on merely being added to acetylacetone in ethyl acetate[34]; the other common secondary amines require heating and/or moderate to severe dehydrating conditions.*

Method (1) thus is attractive on its face, i.e., is worth trying when the starting β-dicarbonyl compound is available or conveniently made. Disadvantages are the possibility of only fair yields and the formation of difficultly separable by-products.

The reaction of vinylogous acid chlorides with amines (Method (2)) has been used extensively to obtain vinylogous amides.[39] Yields are often fair to good, and the starting ketones can usually be prepared in good yield by Friedel-Crafts/Darzens' acylation of

---

* Generally, the ease with which secondary amines react with a carbonyl group is in the order pyrrolidine > piperidine, morpholine $\gtrsim$ dimethylamine > diethylamine.[38]

acetylenes or chloroethylenes. Disadvantages are the instability of many β-chlorovinyl ketones, especially the lower aliphatic ones, and the tendency of the starting ketone to vinylogously acylate the desired product (at the α-vinyl carbon).[39]

Aminolysis of vinylogous esters to obtain vinylogous amides has been occasionally employed.[40a] Reaction of 4-methoxy-3-buten-2-one with primary aliphatic amines leads to 2-methyl-5-acetylpyridinium salts by α-vinyl carbon acylation of the intermediate vinylogous amide by the starting material, and subsequent ring closure.[40b] A method for avoiding this further reaction of a vinylogous amide by homogeneous generation of the vinylogous ester in the presence of a large excess of amine will be described in the next section.

The addition of amines to α,β-acetylenic ketones and aldehydes has been used as a route to the subject compounds.[41,42] The ketones can be made by Jones oxidation of the corresponding commercially available alcohols; purification requires careful fractional distillation.[43] This method is, of course, only applicable to open chain compounds.

The study of amine addition to acetylenic <u>esters</u> has been much studied, mostly in connection with attempts to explain the apparent failure of the usually observed <u>trans</u> mode of addition (should lead to <u>cis</u> product).[24,44,45] The explanation, as mentioned previously, lies at least in part in the ready isomerism of <u>cis</u> "push-pull" olefins to the more stable <u>trans</u> compounds.[18,46]

The acylation of enamines (Method (4)) has been an extensively explored reaction since its general synthetic utility was shown by Stork and co-workers.[11-13] The vinylogous amides resulting from the aceylation have often been hydrolyzed to β-dicarbonyl compounds without isolation of the intermediate initial acylation product.[11,12a,47] There is, therefore, a paucity of data on the intermediates.

The utility of this method depends on the ready availability of the unacylated enamines. Since enamines of lower aliphatic ketones are usually prepared with difficulty,[48] this method is attractive principally for enamines derived from cyclic ketones (Type II above) and from aldehydes. A complication encountered when acylating an enamine using an acid chloride with at least one α-hydrogen in the presence of an auxiliary base (e.g., triethylamine) is that a ketene may be the actual acylating reagent. This results in the initial formation of the cycloaddition product, an aminocyclobutanone. This intermediate can ring open to give an isomer of the desired acylation product.[49] This phenomenon will be discussed more fully in the next section in connection with the acylation of an aldehyde-derived enamine.

Syntheses--Results and Discussion

Introduction. The last section was organized by methods of synthesis. In this section, the discussion will be organized by the type of compound, as defined above, with the emphasis on describing a satisfactory way to make a given type of compound rather than on how efficient and convenient a given method is. In some cases for which a variety of methods was employed, the latter question is of course answered incidentally.

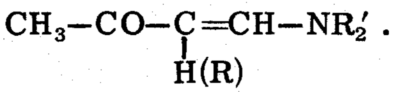
3-N-Pyrrolidino-2-cyclohexenone(1) (Type I). This compound was obtained in ~ 75% crude yield by refluxing 1,3-cyclohexanedione-(3-hydroxy-2-cyclohexenone, dihydroresorcinol) with ~ 65% excess of pyrrolidine in benzene. The reaction was followed by monitoring the amount of water generated (graduated water separator under reflux condenser); the theoretical quantity separated in about one hour. It is important to drive this reaction to completion since the starting diketone is hard to separate from the desired product. Much tarring occurred during the reaction. The product was purified by an unusual recrystallization procedure: The crude material was taken up in benzene and the brown *impurities* were precipitated by adding ether little by little with frequent filtration.[32] When white crystals appeared, the solvents were stripped and the product recrystallized several times from ethyl acetate to give nearly white large irregular crystals (~ 60% overall).

The original workers[32] reported that this compound is hygroscopic, gives a low analysis for carbon and nitrogen, and melts at 84-88°. The first two observations suggest contamination with the pyrrolidinium salt of the diketone anion. My purified samples were stable for at least two years with no special precautions. I found melting points of 45-45° and 53-55° (hot stage). Polymorphism is evident in the solid from the fact that when the *same* capillary melting point sample was repeatedly melted and allowed to re-solidify, the melting point rose eventually to 83-84°.

1-Acetyl-2-diethylaminocyclopentene(2) (Type II). This compound was obtained by the reaction of acetyl chloride with the cyclopentanone enamine, 1-diethylaminocyclopentene, using triethylamine as an auxiliary base. The diethyl compound was chosen for its ease of preparation and the simplicity of its nmr spectrum, although it cannot be made in as good a yield as enamines derived from cyclic secondary amines.[11,50] It was hoped that clearly nonequivalent N-ethyl protons due to restricted rotation around the ring-nitrogen bond would be observed in the acylated product; only moderate broadening was observed.

The use of triethylamine in the acylation is necessary to prevent loss of half the enamine as the hydrochloride since the enamine is a stronger base than the vinylogous amide product. With common ring ketone enamines, the fact that ketene is the actual acylating agent does not lead to abnormal products.[49]

The vinylogous amide 2 is less sensitive than the starting enamine to moisture and air. Distilled material stored two years at 0-5 ° discolored only slightly.

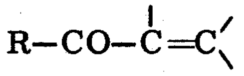
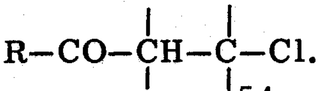
4-(Dialkylamino)-3-buten-2-ones (Type III). A number of these compounds were made, both with α-vinyl hydrogen and alkyl,  $CH_3-CO-\underset{H(R)}{\underset{|}{C}}=CH-NR_2'$. Two reasons for preparing a series of these compounds (although only the simplest, 4-dimethylamino-3-buten-2-one was ultimately used as a ligand) were (1) to make both a *cis* and *trans* open chain vinylogous amide, and (2) to have model compounds of known stereochemistry to determine the stereochemistry of the enamino ketones derived from acetylacetone, the 4-dialkylamino-3-penten-2-ones.

The first reason is now known to be illusory in view of above discussion concerning stereochemistry and the facile *cis-trans* isomerism of the subject compounds. Some of the spectral results discussed below are suggestive of conformational differences among the β-dialkylamino butenones. But for no compound were stereomers detected, and the evidence indicates that all the species are *trans*. However, the second purpose was partially fulfilled.

My hope for gaining some stereochemical insight regarding these compounds lay in the premises that (a) a configuration assignment could be made with reasonable confidence for the compounds with both α- and β-vinyl hydrogens on the basis of the nmr coupling constant alone even if only one isomer is present, and (b) that in stereoisomers and in compounds with the same functionality, a β-vinyl proton *cis* to a carbonyl group has its nmr chemical shift at substantially lower field (usually 0.5-1.0 ppm) than does one which is *trans* (deshield-effect of a proximal carbonyl).[45,51] When the compounds with α-vinyl hydrogen or methyl were found to be *trans*, I attempted to made a *cis* compound by having a bulky α-vinyl group (isopropyl). At the time this last effort was underway, it became clear that the goal was essentially pointless, further attempts to make an open chain *cis*-dialkylenamino ketones were abandoned.

4-Dimethylamino-3-buten-2-one (**3**) was prepared by the following methods: (1) reaction of sodio formylacetone with dimethylammonium chloride[25] (Method (1)); (2) reaction of a mixture of *trans*-4-chloro-3-buten-2-one and 4,4-dichloro-2-butanone with dimethylamine[42] (Method (2)); and (3) addition of dimethylamine to methyl ethynyl ketone.[41]

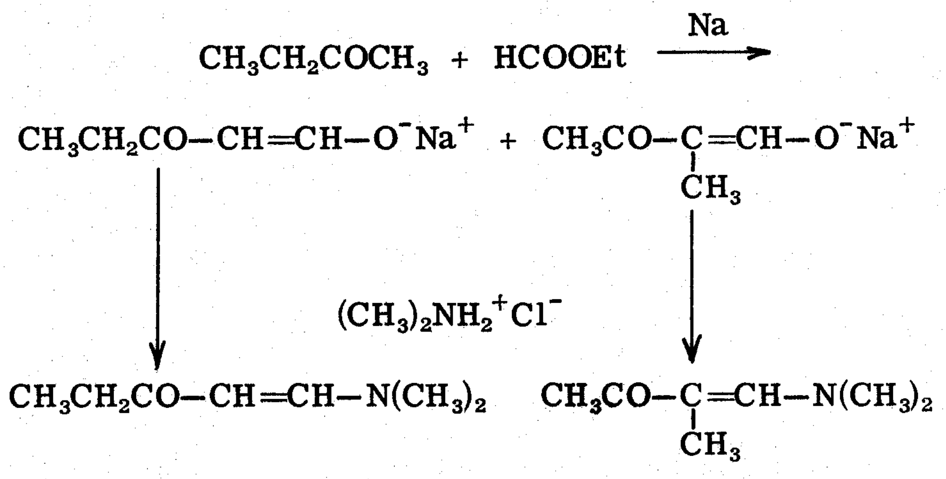
All three methods gave only *one* stereomeric product (nmr assay of crudes), having $\delta \sim 5.0$ (d, J= 13 Hz, α-vinyl H) and ~ 7.0 (d, J = 13 Hz, β-vinyl H). The chemical shift is quite solvent sensitive but was always the same for all samples under the same conditions. The value of the coupling constant implies the *trans* configuration.[23a, 24] This finding is consistent with the report that addition of piperidine to methyl propiolate gives initially only ten percent *cis*-enamino ester, which rapidly isomerizes completely to the *trans* isomer.[52]

Some comments about the syntheses of the enamino ketone **3** by methods (2) and (3) are appropriate. In my hands, the Friedel-Crafts/Darzens acetylation of vinyl chloride without *steam* distillation of the product(s) always yielded a mixture of *trans*-$ClCH{=}CH{-}CO{-}CH_3$ and $Cl_2CH{-}CH_2{-}COCH_3$; only the unsaturated ketone is obtained if the crude product is steam distilled (90% yield).[53] The pure unsaturated ketone could be frozen out of the mixture (mp ~ 10°), but this was not necessary for the reaction with dimethylamine. In the reaction, *all* of the chlorine was precipitated as dimethylammonium chloride. What probably occurs is that the amine dehydrochlorinates the saturated ketone to the unsaturated one, which then undergoes substitution. That this elimination-substitution sequence is at least possible is shown by the fact that even feebly basic amines such as semicarbazide give the normal derivatives of  $R{-}CO{-}\overset{|}{C}{=}C\!\lessdot$ on reaction with  $R{-}CO{-}\underset{|}{\overset{|}{C}}H{-}\underset{|}{\overset{|}{C}}{-}Cl$.[53] The elimination of HCl is a typical facile β-elimination.[54]

With respect to method (3), I found that the presence of a small amount of the unoxidized alcohol from which methyl ethynyl ketone was made does not interfere with the reaction of the latter with dimethylamine. The amine does not react with the alcohol under mild conditions; in fact it is easier to separate the product vinylogous amide **3** from the alcohol than to separate the starting ketone from the alcohol.

4- Dimethylamino-3-methyl-3-buten-2-one (**4a**) was prepared by Method (1), viz., the reaction of the sodium salt of formyl methyl

ethyl ketone with dimethylammonium chloride. The crude product was a 4:3 mixture of **4a** and an isomer derived from the formylation of methyl ethyl ketone at the methyl rather than the methylene[28]:



$$CH_3CH_2COCH_3 + HCOOEt \xrightarrow{Na}$$

$$CH_3CH_2CO-CH{=}CH-O^-Na^+ \quad + \quad CH_3CO-\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH-O^-Na^+$$

$$\Big\downarrow \quad (CH_3)_2NH_2^+Cl^- \quad \Big\downarrow$$

$$CH_3CH_2CO-CH{=}CH-N(CH_3)_2 \qquad CH_3CO-\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH-N(CH_3)_2$$

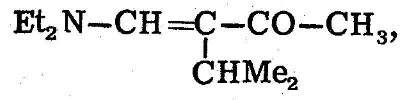
4b **4a**

Pure **4a** is readily frozen out of the isomeric mixture.

In the mixture, the chemical shift of β-vinyl proton in **4a** is only ~ 0.2 ppm to higher field than is that of its structural isomer **4b**, which is definitely *trans* (J = 13 Hz). For pure **4a**, the β-vinyl proton shift is at nearly the same value as that of the homologous definitely *trans* compound **3**. On these bases, and because the chemical shift difference for the same proton in *cis* and *trans* 4-*mono*methylamino-3-methyl-3-buten-2-one is 0.7 ppm,[1b] **4a** is assigned the *trans* configuration.

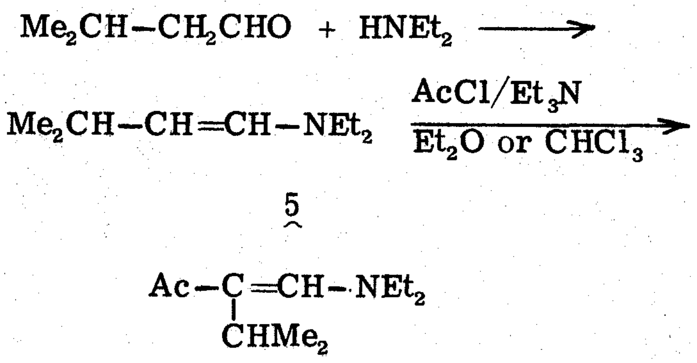
The nmr signals from the two C-methyls in **4a** are 0.2 ppm apart. In conformity with an earlier assignment and the calculated presence of a partial negative charge at the α-vinyl carbon,[1b] the lower field absorption is assigned to the acetomethyl. The allylic coupling constant in 4a and generally in enamino ketones with alkyl at either the α- or β-vinyl carbon is nil. I estimate that a splitting as large as 0.5 Hz would be detectable.

The β-aminobutenone with the largest α-vinyl substituent, viz., 4-diethylamino-3-(2-propyl)-3-buten-2-one (6a)



$\mathrm{Et_2N{-}CH{=}}\underset{\displaystyle\mathrm{CHMe_2}}{\mathrm{C}}\mathrm{{-}CO{-}CH_3}$,

was prepared by acylation of the diethyl enamine of isovaleraldehyde:



$$\mathrm{Me_2CH{-}CH_2CHO} + \mathrm{HNEt_2} \longrightarrow$$

$$\mathrm{Me_2CH{-}CH{=}CH{-}NEt_2} \xrightarrow[\mathrm{Et_2O\ or\ CHCl_3}]{\mathrm{AcCl/Et_3N}}$$

5

$$\mathrm{Ac{-}}\underset{\displaystyle\mathrm{CHMe_2}}{\mathrm{C}}\mathrm{{=}CH{-}NEt_2}$$

6a

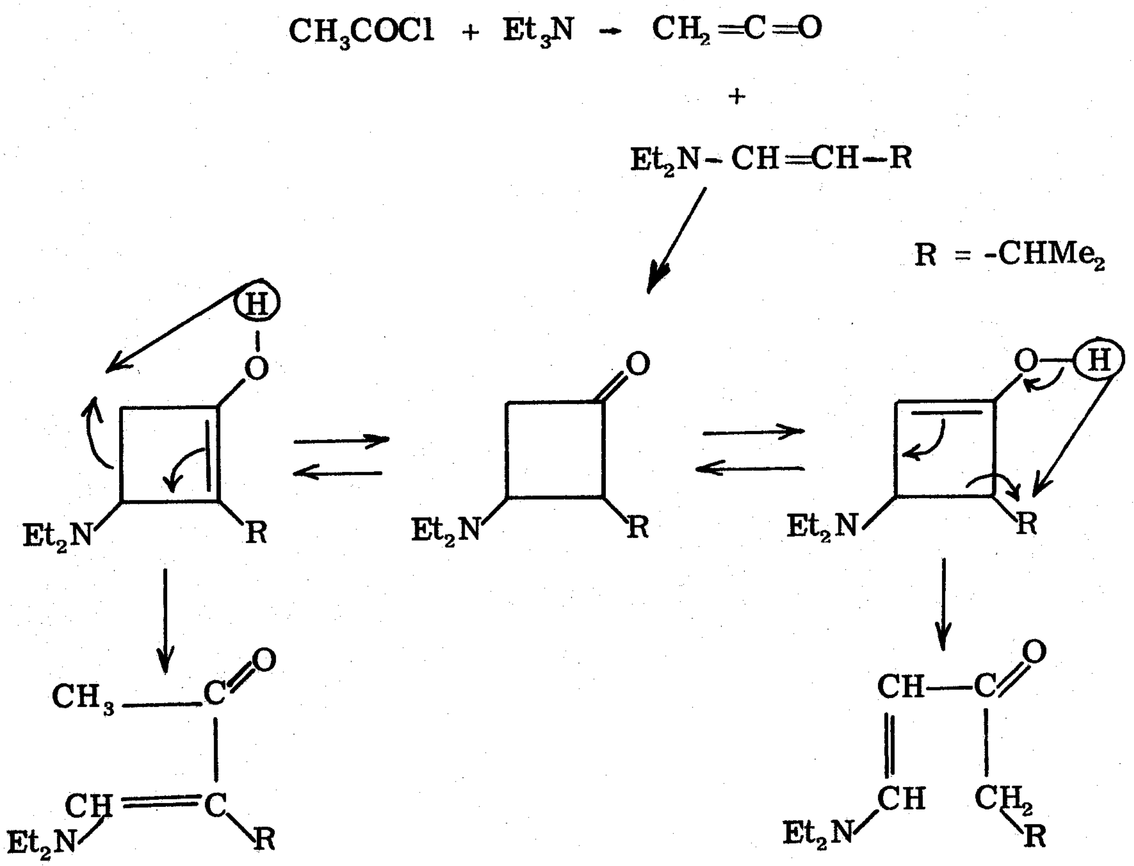
The compound 6a cannot be made by the method used to prepare the 3-methyl compound 4a since Claisen formylation of methyl isobutyl ketone gives nearly exclusively the product formylated at the α-methyl rather than the α-methylene.[55]

The enamine 5 was readily formed directly from isovaleraldehyde and excess diethylamine in the presence of anhydrous potassium carbonate.[56] No evidence for intermediate aminal formation was found.[57] The nmr spectrum shows the two olefinic protons at δ 3.75 and 5.50. The *trans* configuration is indicated by

$J_{olefinic} = 14$ Hz. That the high field absorption is due to the β-vinyl hydrogen is shown by its coupling with the methine proton ($J = 7$ Hz). The very high field location of this absorption for an olefinic proton is understandable when it is realized that it is vinylogously an amine hydrogen. The allylic coupling of the α-vinyl and methine hydrogens is just observable with an A-60A spectrometer, $J = 0.6$-0.8 Hz.

Acylation of the enamine 5 to yield the desired vinylogous amide 6a was not as straightforward as anticipated. As performed, two olefins, 6a and 6b, were formed in approximately a 3:1 ratio. The nmr spectrum of the major product, 6a, had a singlet absorption at δ 6.92 in the mixture. The minor product, 6b, shows two doublets at δ 4.96 and 7.38 ($J = 13$ Hz). These latter absorptions are suggestive of a *trans*-$R_2N{-}CH{=}CH{-}CO{-}R'$ moiety.

Analogous results with similar systems have been explained by invoking the intermediacy of a ketene, its cycloaddition with an enamine to form a β-dialkylaminocyclobutanone, and two competitive modes of ring opening of the latter.[58] This mechanism adapted to the route from 5 to 6a and 6b is as shown below (proton transfers are depicted as intramolecular for convenience):



6a

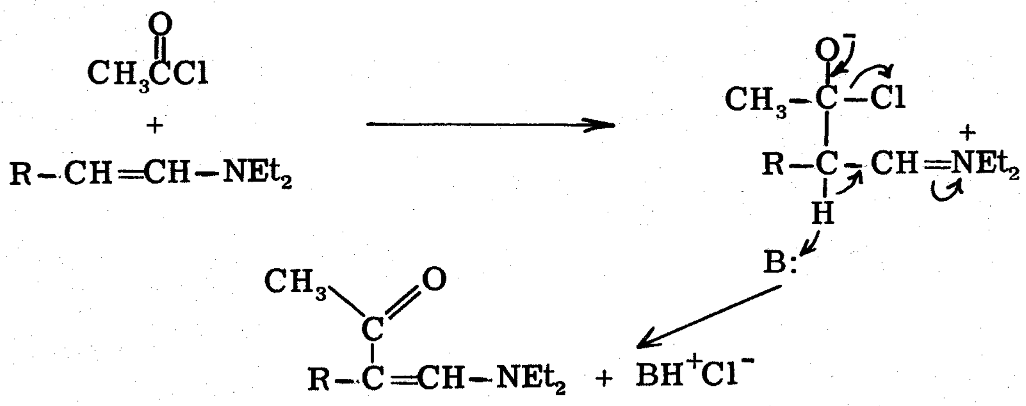
"normal" product

6b

"abnormal" product

(Product structures not intended to be geometrically accurate.)

The cyclobutanone intermediate is of course not necessary to explain the formation of the "normal" product 6a, which can arise by a simple acylation mechanism:

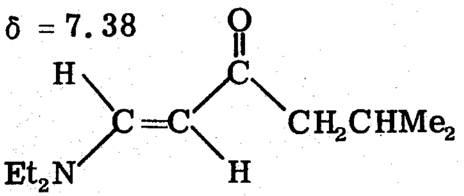


In the reaction of ketene with the morpholine enamine of butyraldehyde, the "abnormal" product was formed predominantly.[59] The contrast between this result and that just described (3:1 ratio of "normal" to "abnormal" product) suggests that part of 6a may arise from simple acylation rather than cycloaddition and ring cleavage.

The isomeric aminobutenones 6a and 6b were separated by vacuum fractional distillation; 6a is lower boiling. No attempt was made to obtain 6b pure.

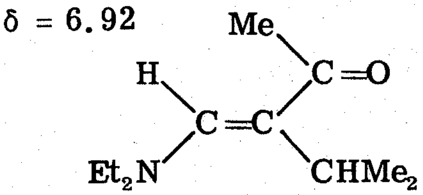
The spectral evidence indicates that both 6a and 6b have their functionality *trans*. The straight chain compound 6b has an olefinic coupling constant of 13 Hz, as do 3 and 4b. The α-isopropyl compound 6a shows nearly the same chemical shift value for its β-vinyl hydrogen as do 3 and the α-methyl compound 4a. The allylic J value for 6a is nil (<0.5 Hz) as it is for 4a. Further nmr evidence that 6a is not *cis* s found in the nearly isosynchrous values of the chemical shifts of th the α- and β-N-ethyl protons for the two isomers, 6a and 6b.

The explanation for the 0.46 ppm lower field absorption of the β-vinyl proton of 6b compared to 6a probably lies in part in a conformational difference. The use of models and ir spectral data show that for straight chain β-enamino ketones, such as 3, 4b, and 6b, the s-cis conformer is progressively more favored as the carbonyl substituent becomes larger.[23a] Conversely, a bulky α-vinyl substituent favors the s-trans conformation.[60]



6b

s-cis favored



6a

s-trans favored

6a shows a single carbonyl absorption, suggesting the presence of only one conformer.[23a,b]

The point of this conformational analysis is that it is reasonable that the β-vinyl proton absorbs at lower field in 6b than in 6a on the basis of the position of the carbonyl.[16,51] Steric considerations also indicate (in retrospect!) the probable futility of compelling a cis configuration by use of a large α-vinyl substituent. Cis 6a would have to have the enamino carbonyl system highly skewed, inhibiting conjugation; this fact has been observed for other open chain enones substituted at both olefinic sites.[61]

A final aspect of this section was the brief exploration of a simple one-step route to the straight chain β-aminobutenones, $>$N$-$CH$=$CH$-$COCH$_3$. Toward the end of the synthetic efforts described above, I became aware of the cheap commercial availability of the β-ketoacetal, (Me$_2$O)CH$-$CH$_2-$COCH$_3$ (7).[62] This compound is in equilibrium with the vinylogous ester 8 in the presence of base,[63]

$$\underset{7}{(\mathrm{MeO_2})\mathrm{CHCH_2Ac}} \overset{\text{base}}{\rightleftharpoons} \underset{8}{\mathrm{MeO{-}CH{=}CH{-}Ac}} + \mathrm{MeOH}$$

Since the vinylogous ester 8 might reasonably be expected to be <u>irreversibly</u> aminolyzed (as are ordinary esters),

$$>\mathrm{NH} + \underset{8}{\mathrm{MeO{-}CH{=}CH{-}Ac}} \longrightarrow$$

$$>\mathrm{N{-}CH{=}CH{-}Ac} + \mathrm{MeOH},$$

I hoped that heating on amine with the acetal 7 would effect the overall reaction, the amine itself serving as the base to establish the equilibrium between 7 and 8.

The hoped-for result was obtained. With t-butyl- and diethylamine and pyrrolidine, refluxing a two- to three-fold excess of the amine with the acetal 7 for 24-48 hours gave total conversion and 70-80% yields of the vinylogous amides. The tertiary nitrogen compounds are as usual a single isomer (trans). The N-t-butyl compound (9) (white solid) showed both stereoisomers, as does the

N-*mono*methyl one.[1b] In CCl_4, **9** is ~95% *cis*, *s-cis* (chelated N—H---O); in ethanol the *cis*, *trans* ratio is ~5:2. In both solvents, the β-vinyl H of *cis*-**9** is a doublet of doublets, with somewhat broader peaks in ethanol, implying slow exchange in this solvent. For *trans*-**9** in ethanol, the β-vinyl H is a quite broad doublet, implying fast exchange of the N—H and some exchange of the α-vinyl H. In the crude reaction mixture, which has excess amine, the vinyl H's of *trans*-**9** are only slightly broadened doublets. The chemical shift differences for the corresponding protons in the two stereomers are ~0.60 ppm for the β-vinyl H's and ~0.32 ppm for the α-vinyl ones. Both these values are slightly larger in ethanol. For both protons, those of the *cis* isomer are to higher field.

In following the progress of the reactions by nmr, no evidence for the vinylogous ester **8** or any other intermediate was found. Thus the proposed mechanism is not proved; a possible alternate one would be displacement of a methoxyl followed by elimination of methanol. The latter seems to me unlikely in view of the fact that methoxyl is generally a poor leaving group in simple SN_2 displacements.

The reaction of **7** with amines is slow at room temperature. With a three-fold excess of diethylamine standing at ~23°, about 40% conversion of **7** to 4-diethylamino-3-buten-2-one was effected in 18 days (nmr assay). Assuming the reaction to be applicable to the lower volatile amines, it would require sealed tube apparatus.

In the reaction of *t*-butylamine, no pyridine derivative was detected, although the reaction of primary aliphatic amines with the vinylogous ester 8 gives pyridinium compounds.[40b] My results may mean either that 8 is not an intermediate or that with excess amine, 8 is aminolyzed much more rapidly than it reacts with the vinylogous amide product.

Under the conditions used for aliphatic amines, reaction of 7 with aniline gives heavy tarring and slow generation of methanol at ~180°. This probably reflects the lower basicity of aniline in solution compared to aliphatic amines. However, from a stoichiometric mixture of the vinylogous ester 8 and aniline allowed to stand 12 hours at room temperature, an 84% yield of 4-anilino-3-buten-2-one precipitated as an off-white solid.

Thus, the reaction of the β-ketoacetal 7 with aliphatic amines to yield β-aminobutenones is probably general. Its attractiveness as a synthetic method lies in the ready availability of the starting materials, its convenience and good yields, and the freedom from difficultly separable by-products.[64]

4-Dialkylamino-3-penten-2-ones (Type IV). These compounds are generally accessible through reaction of acetylacetone (10) with a secondary amine.[33-35] Three were prepared, R_2N= piperidino (11), dimethylamino (12), and pyrrolidino (13). Each consisted of a single stereoisomer. Pure samples (white solids) stored at 0-5° under nitrogen were stable for at least several years.

The vinylogous amide 11 was obtained by refluxing 10 and piperidine in benzene or toluene. Even without continuous separation of water, 60-70% crude yields were obtained. The dimethylamino analog 12 was made similarly except that a sealed flask was maintained at ~60° for 24-48 hours and 2,2-dimethoxypropane with a little HCl was used as the solvent to facilitate dehydration.

The pyrrolidine compound 13 is the easiest tertiary vinylogous amide to prepare and purify. It precipitates in ~70% yield on adding the amine to 10 in ethyl acetate and allowing the solution to stand a few hours. Recrystallization from EtOAc affords pure (i.e., white) material with high recovery, obviating the need for a cleansing distillation.

Dimethyl- and diethylamine and piperidine give only their salts with 10 under the conditions used to make 13 (nmr shows equivalent C-methyls and a broad N/O-bound hydrogen absorption).

The β-aminopentenones, 11, 12, and 13, all have the *trans** configuration as judged by their nmr spectra. This conclusion rests on two pieces of data:

(1) The closeness of the chemical shift values for the protons of the amine part of the molecule in 12 and 13 and those of the corresponding *trans*-β-aminobutenones, and (2) the large chemical shift difference between the two C-methyls in 11 - 13 (4-methyl to lower field) compared to that found in *cis*-4-alkylamino-3-penten-2-ones.[1c] The relevant data are set out below.

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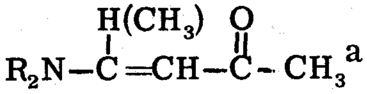
*The designation refers to the relation of the amino and acetyl groups. This violates the longest-carbon-chain rule; it is adopted so that the same word describes the same steric relationship of the *functionality* for these compounds a

Table I

Proton Resonance Data for
4-Dialkylamino-3-penten-2-ones and
Related *Trans*-Aminobutenones,



$$R_2N-\overset{\overset{H(CH_3)}{|}}{C}=CH-\overset{\overset{O}{\|}}{C}-CH_3$$[a]

Compound	α-vinyl H	C-methyls	α-amino	β-amino
11 ($C_5H_{10}N$-)	5.24	2.06, 2.50	3.35[b]	1.59[b]
12 (Me_2N-)	5.00	2.00, 2.45	2.95	
3, *trans*-$Me_2N-CH=CH-Ac$	5.08	2.08	2.93	
13 (C_4H_8N-)	4.93	2.01, 2.48	3.30[b]	1.93[b]
14, *trans*-$C_4H_8N-CH=CH-Ac$	5.05	2.10	3.33[b]	1.97[b]

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[a] δ values in $CHCl_3$.

[b] Center of complex signal.

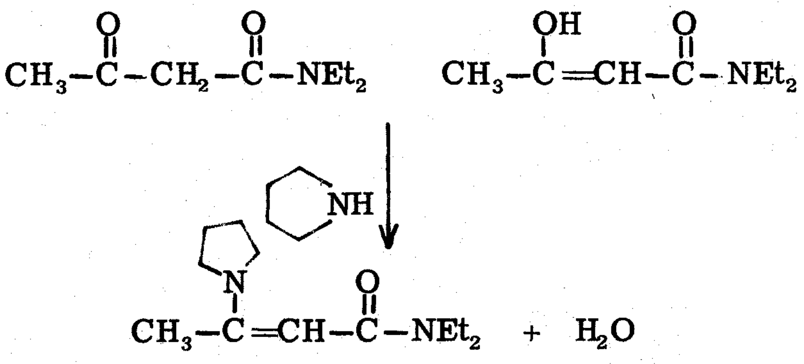
With respect to the first argument, the nearness of the δ values for corresponding amine moiety protons between **12** and **3**, and **13** and **14**, suggests the same configuration. Were **12** and **13** *cis*, one would expect absorption to lower field from the deshielding effect of the carbonyl,[16,51] especially since **11**-**13** are *s*-*cis* regardless of the configuration.[23a]

With regard to the second contention, the wide separation of the C-methyls in **11**-**13** (~0.4 ppm) and the low field absorption of one of them strongly suggests that the one at δ 2.45-2.50 is the 4-methyl deshielded by the *cis*-carbonyl. In *cis*-enaminoketones derived from acetylacetone, both C-methyls fall in the range δ 1.9-2.1 in CCl_4 and $CHCl_3$,[1c] as does the acetomethyl in the β-aminobutenones. Thus, I contend that the low field C-methyl is in fact the β-vinyl one with its position due to the fact that it is *cis* to the carbonyl, requiring that the amino and carbonyl groups be *trans*.

One additional fact bearing on this issue is that I obtained a single compound identical to **13** from reaction of pyrrolidine with a mixture of *cis* and *trans* 4-chloro-3-penten-2-one. Analogous results have been found for the β-chlorocrotonates (only *trans*-β-dialkylamino isomer obtained).[18]

Vinylogous Ureas (Type V). Three compounds of this type, β-aminoenamides, were prepared, all with both nitrogens tertiary.

N,N-diethyl 3-N-pyrrolidino-2-butenamide, $C_4H_{10}N{-}C(Me){=}CH{-}CO{-}NEt_2$ (**15**), was made by refluxing N,N-diethylacetoacetamide (acam) with pyrrolidine in benzene (Method (1)) with continuous water separation.



15

The compound 15 was a high-boiling uncrystallizable oil whose nmr and ir spectra were compatible with the presence of a single species. The possibility that the product is completely or in part the isomeric acetyl ketenaminal formed by amine attack at the amidic rather than the ketonic carbonyl cannot be excluded, although this is unlikely in view of the generally greater reactivity of ketones over amides with nucleophiles. Amine exchange might also occur in this system.

The two other vinylogous ureas prepared were made by aminolyzing vinylogs of phosgene (i. e., β-chloroenoyl chlorides) and with the same amine (piperidine) at both ends to avoid the above ambiguities. In this way was prepared trans-$C_5H_{10}N-CH=CH-CO-NC_5H_{10}$ (16) by the following sequence[45, 65]:

$$\text{HOOC}-\text{C}\equiv\text{C}-\text{COO}^-\text{K}^+ \xrightarrow[\text{-CO}_2]{\text{heat in H}_2\text{O}}$$

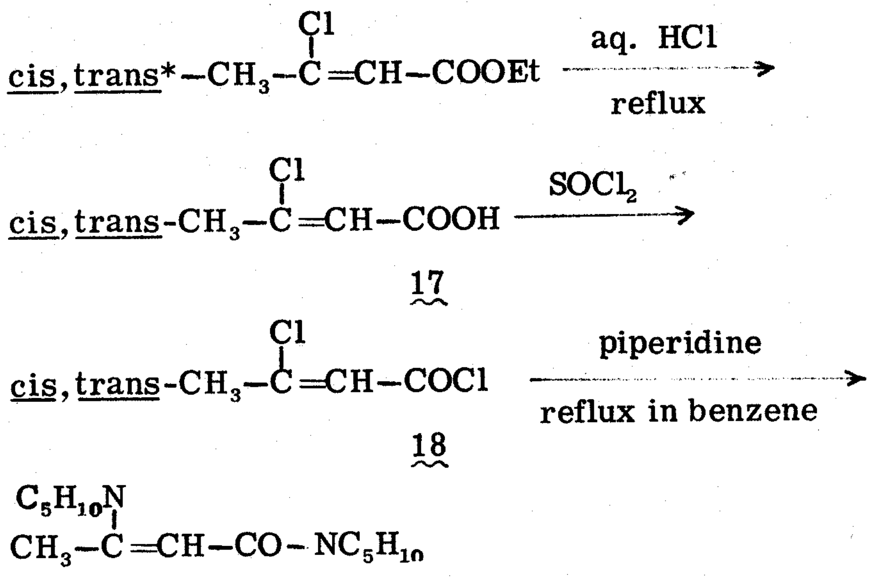
$$\text{HC}\equiv\text{C}-\text{COO}^-\text{K}^+ \xrightarrow[\text{heat}]{\text{conc. HCl}}$$

$$\underline{\text{trans}}\text{-ClCH}{=}\text{CH}-\text{COOH} \xrightarrow[\text{distill}]{\text{BzCl}}$$

$$\underline{\text{trans}}\text{-ClCH}{=}\text{CH}-\text{COCl} \xrightarrow[\text{ether, R.T.}]{\text{piperidine}} \quad 16$$

Also prepared was the β-methyl homolog of 16, $C_5H_{10}N-C(CH_3){=}CH-CO-NC_5H_{10}$ (19), as follows[66]:

$$\text{CH}_3-\text{CO}-\text{CH}_2-\text{COOEt} \xrightarrow[\text{benzene}]{\text{PCl}_5}$$



$$\underline{\text{cis}},\underline{\text{trans}}^{*}-\text{CH}_3-\overset{\text{Cl}}{\overset{|}{\text{C}}}{=}\text{CH}-\text{COOEt} \xrightarrow[\text{reflux}]{\text{aq. HCl}}$$

$$\underline{\text{cis}},\underline{\text{trans}}\text{-CH}_3-\overset{\text{Cl}}{\overset{|}{\text{C}}}{=}\text{CH}-\text{COOH} \xrightarrow{\text{SOCl}_2}$$

17

$$\underline{\text{cis}},\underline{\text{trans}}\text{-CH}_3-\overset{\text{Cl}}{\overset{|}{\text{C}}}{=}\text{CH}-\text{COCl} \xrightarrow[\text{reflux in benzene}]{\text{piperidine}}$$

18

$$\text{CH}_3-\overset{\text{C}_5\text{H}_{10}\text{N}}{\overset{|}{\text{C}}}{=}\text{CH}-\text{CO}-\text{NC}_5\text{H}_{10}$$

19 (one isomer)

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*Designates steric relationship of β-chlorine and carbonyl.

The conversion of the stereoisomeric acids **17** to the acid chlorides **18** proceeded with retention of configuration with $SOCl_2$. Other workers have reported obtaining the *trans* acid chloride from the *cis* acid with PCl_5,[67] and partial conversion of *cis*-3-chloropropenoic acid to the *trans* acid chloride with PCl_3.[45] For the chlorides **18**, the *trans* isomer was lower boiling; similar behavior has been found for esters of **17** and the esters and acid chlorides of the 3-chloropropenoic acids.[18,45] Nmr assay of the mixed acids **17** and acid chlorides **18** is easy since the chemical shift difference of the β-methyls is 0.34 ppm for the isomers of **17** and 0.25 ppm for those of **18**. The *trans* isomer (methyl *cis* to carbonyl) has the lower field absorption, as expected.[18] The α-vinyl proton resonances are nearly isosynchronous for the two acids **17** (*cis* isomer has signal to slightly higher field), and overlap for the isomers of **18**. Allylic coupling is detectable for all four compounds.

The obtaining of a single species **19** from piperidine and the mixed **18**'s is not surprising in view of the previous discussion. The allylic J was nil as for all the "push-pull" olefins.

The acyl chlorine in **18** is replaced much more rapidly than the vinyl one. The first-formed β-chloroenamides are vinylogous carbamyl chlorides, which by analogy to the reactivity of carbamyl compared to acyl chlorides, react sluggishly with nucleophiles. Thus the mixed **18**'s reacted rapidly with two moles of diethylamine to give the β-chloroamides with complete retention of the olefin configuration.

At room temperature, further reaction with added excess amine was very slow. Therefore in the reaction to make the piperidine compound 19, the initially formed amides were refluxed with excess amine in benzene for 24 hours; this afforded complete reaction to yield the vinylogous urea 19.

Heating was not necessary to effect total conversion of *trans*-ClCH=CH—COCl to the vinylogous urea 16; this acid chloride is less hindered at the β-vinyl carbon than is 18.

The vinylogous ureas 16 and 19 each have two sets of *magnetically* non-equivalent α-piperidino protons. The significance of this will be discussed in Chapter II in connection with the reaction of piperidine with β,β-dichlorovinyl carbonyl compounds.

Experimental

General. Starting materials were readily available commercial products unless otherwise noted. Infrared spectra were taken on a Perkin-Elmer 225 grating infrared spectrophotometer, usually on 50 mg/ml solutions in 0.1 mm KBr cells. The assignment of the higher frequency absorption(s) in the double bond stretching region to the carbonyl for vinylogous amides follows literature precedents.[23a, 34] It is recognized that the C=O and C=C stretching modes are strongly coupled in these compounds.[23a] Nmr spectra were taken on a Varian A-60A analytical nmr spectrometer.

3-N-Pyrrolidino-2-cyclohexenone (1). The procedure described below is an expanded version of the literature preparation.[32]

In a flask with a reflux condenser and graduated water separator, a mixture of 69.4 g 97% 1,3-cyclohexanedione (0.6 mol, light tan powder) and 580 ml benzene was brought to a boil to effect solution and allowed to cool. To this orange solution was added over 5 minutes 85 ml (1.0 mol) pyrrolidine (exothermic reaction and darkening). The solution was refluxed for 1 hour; 11.5 ml (0.64 mol, 107%) water separated. The solution was filtered hot, stripped on a rotary evaporator, cooled to ~ 0°, and 77 g (78%) brownish crystals were filtered off. Repeated recrystallization from EtOAc always gave material with adherent brown gum. Fifty grams of this material was dissolved in 60 ml benzene, and as ether was added in small portions, brown gum precipitated, which was repeatedly filtered off. After ~ 180 ml ether had been added, white crystals began to precipitate. The solution was then stripped, and the resulting yellowish solid recrystallized twice from EtOAc (~ 0.5 ml/ g of crude). This afforded 37 g (57% overall, adjusted) nearly white irregular crystals. Mp 83-84° (see discussion) [lit. mp 84-8°,[32] 81-82°[34]]; ir (CCl_4) 1625 (s, C=O), 1564 cm^{-1} (us, C=C); (CH_2Cl_2) 1606, 1556 cm^{-1}; ($CHCl_3$) 1600, 1552 cm^{-1}; nmr (CCl_4) δ ~ 1.95 (m, 8, β-pyrrolidno H's and two $-CH_2-$ in six-membered ring), 2.39 (distorted triplet, 2, J= 7 Hz, one $-CH_2-$ in 6-ring), 3.29 (broad, 4, α-pyrrolidino H's), 4.68 (s, 1, vinyl H).

1-Acetyl-2-diethylaminocyclopentene (2). The enamine, 1-diethylaminocyclopentene was prepared as described by Blanchard.[50] Stirring 211 ml cyclopentanone (2.5 mol), 450 ml diethylamine (4.4 mol) with 190 g anhydrous 12-mesh $CaCl_2$ in 400 ml ether for seven days at room temperature under nitrogen yielded after filtration, stripping at reduced pressure, and fractionation through a 30-cm Vigreux column a forerun of 93 g cyclopentanone (implies 55% converted) with a little Et_2NH and 88 g (46% based on unrecovered ketone) enamine, bp 79-81 ° (23 mm) [lit.[50] bp 99-101 ° (60 mm)]. Ir (CCl_4) 1620 cm^{-1} [lit.[50] 1640 cm^{-1} in ether]; nmr (neat) δ 0.78 (t, 6, J = 7 Hz, CH_3's), ~ 1.7 and ~ 2.1 (broad distorted multiplets, 6, ring $-CH_2-$'s), 2.76 (q, 4, J = 7 Hz, amino $-CH_2-$'s), 3.88 (m, 1, vinyl H).

The acetylation of the enamine was done by a modification of a standard procedure.[68]

To a solution stirring in an ice bath of 106 g (0.76 mol) 1-diethylaminocyclopentene and 115 ml (0.80 mol) triethylamine in 600 ml dichloromethane was added over 90 minutes 56 ml (0.77 mol) acetyl chloride in 100 ml CH_2Cl_2. After stirring one hour in ice, the mixture was stirred 18 hours at room temperature. The resulting slurry of white solid in a red solution was stripped, 200 ml ether was added, and the white solid filtered off and washed with ~ 200 ml ether, leaving 104 g (98%) triethylammonium chloride. Stripping the ether solution afforded 138.4 g (101%) crude product as a brown oil. Two distillations at oil pump vacuum taking a narrow boiling range center cut during the second afforded 82.4 g (60%) of 2 as a pale yellow liquid, bp 81-85° (0.8 mm), ~ 95% mole % by nmr. At water aspirator vacuum, ~ 80% of the crude distilled 138-150° (18 mm) but was quite discolored; this procedure was used for preliminary purification in one run. Ir (CCl_4) 1633 (s, C=O), 1531 cm^{-1} (s, C=C); ir (CH_2Cl_2) 1620 (s, C=O), 1526 cm^{-1} (s, C=C). Nmr (neat) δ 1.81 (t, 6, J = 7 Hz, $C\underline{H}_3CH_2N$-), 1.48 (distorted triplet, 2, J ~ 7 Hz, 4-methylene), 1.76 (s, 3, $C\underline{H}_3CO$), ~ 2.4 (broad multiplet, 4, 3- and 5-methylenes), 3.18 (q, 4, J = 7 Hz, $CH_3C\underline{H}_2N$-).

4-Dimethyl-3-buten-2-one (3).

Method (1). Sodio formyl acetone was made by essentially the classic method.[26] To a cold stirring suspension of 23 g (1.0 mol) sodium chips (3-4 mm) under 400 ml dry ether was added dropwise over 30 minutes a mixture of 80 ml (1.10 mol) acetone and 92 ml (1.12 mol) ethyl formate with a few drops of anhydrous ethanol. After the addition, the mixture was stirred 20 minutes in ice and then 12 hours at room temperature; all the sodium had been converted to a yellow powder. This was filtered off, washed with ether, and dried *in vacuo* to afford 88.3 g (81%) of the sodium salt.

A modification of the method of Benary[25] was used to prepare 3. To a stirring suspension of 40 g (0.37 mol) sodio formyl acetone in 200 ml absolute ethanol and 50 ml (~ 0.4 mol) 2,2-dimethoxypropane was added at 25° a solution of 34.5 g (0.42 mol) dimethylammonium chloride in 175 ml absolute EtOH. The suspension was stirred for 18 hours, the sodium chloride filtered off and washed through with ether, and the solution stripped. Distillation of the resulting brown oil (44 g, 105%) from K_2CO_3 gave 28 g pale greenish liquid, bp 78-94° (1.3-2.0 mm) which on cooling to 0° afforded 26.4 g (63%) pure 3 as large white spars, mp ~ 25°. Ir (CCl_4) 1668 (s, C=O, *s-cis*), 1618 (s, C=O, *s-trans*), 1582 (s, C=C) [lit.[23a] (C_2Cl_4) 1673, 1623, 1586 cm^{-1}]; nmr (neat) δ 1.61 (s, 3, $C\underline{H}_3CO$-), 2.47 (broad singlet, 6, $C\underline{H}_3N$-), 4.49 (d, 1, J = 13 Hz, α-vinyl H), 6.90 (d, 1, J = 13 Hz, β-vinyl H); nmr ($CHCl_3$) δ 2.08, 2.93, 5.08. 7.47.

Method (2). The Friedel Crafts/Darzens acetylation of vinyl chloride was carried out as described by Catch, *et al.*[53] Bubbling vinyl chloride through a stirring suspension of 133 g (1.0 mol) $AlCl_3$ in 200 ml (large excess) acetyl chloride at 0-10° until weight gain ceased, pouring over ice, extraction with CH_2Cl_2, washing of organic extracts with aqueous $NaHCO_3$, drying, and distilling gave 103 g (~ 85%) of a pale yellow liquid, bp 48-74° (50 mm) which was a 3:1 mixture of *trans*-$CH_3COCH{=}CHCl$ and $CH_3CO{-}CH_2{-}CHCl_2$. Repeated distillation increased the proportion of unsaturated ketone, or it could be frozen out of the mixture (mp 9-11° [lit.[69] mp ~ 5°]) as white spars. Nmr in neat mixture: for $CH_3CO{-}CH{=}CHCl$ δ 1.88 (s, 3, $C\underline{H}_3CO$-), 6.12 (d, 1, J = 14 Hz, α-vinyl H), 7.07 (d, 1, J = 14 Hz, β-vinyl H); for $CH_3CO{-}CH_2{-}CHCl_2$ δ 1.79 (s, 3, $C\underline{H}_3CO$), 3.09 (d, 2, J = 6 Hz, $CO{-}C\underline{H}_2$), 5.83 (t, 1, J = 6 Hz -$C\underline{H}Cl_2$).

To a mixture of the above chloroketones which contained 70.9 g (0.68 mol) olefinic ketone and 21.4 g (0.15 mol) saturated ketone in 400 ml dry ether was added dropwise over 40 minutes at 0-7° a solution of 95 ml (1.43 mol) dimethylamine in 150 ml ether. After stirring 4 hours in ice, the solution was allowed to warm, and 80.0 g (100% based on all chlorine in both ketones) dimethylammonium chloride was filtered off. The nmr spectrum of the stripped ether solution (orange oil) showed none of either starting ketone. Cleansing distillation and freezing of the crude material as described above for Method (1) gave 65.4 g (69%) of 3, with the same properties as material obtained by Method (1).

Method (3). 3-Butyn-2-one was made by Jones oxidation of the alcohol[43]; nmr (neat) δ 1.83 (s, 3, $C\underline{H}_3CO$-), 3.22 (s, 1, $-C{\equiv}C\underline{H}$).

To a solution of 4.1 g (60 mmol) of the acetylenic ketone which had a little of the alcohol in it, in 20 ml ether was added at 0-5°, a solution of 7 ml (106 mmol) dimethylamine in 15 ml ether.[41] After standing in ice for 3 hours, ether and excess amine were stripped off to give 5.14 g (76%) orange oil whose nmr was identical to that of 3 prepared by Method (1).

4-Dimethylamino-3-methyl-3-buten-2-one (4a) and 5-dimethylamino-4-buten-3-one (4b). Methyl ethyl ketone was formylated[70] in a manner analogous to that given above for acetone. Twenty-three grams sodium (1.0 mol), 95 ml (1.05 mol) 2-butanone and 88 ml (1.08 mol) ethyl formate gave 95 g (77%) "sodio formyl methyl ethyl ketone" as a yellow-orange powder, which from the result next described was a mixture of the compounds formylated at the α-methyl and α-methylene of 2-butanone.

This salt was allowed to react with dimethylammonium chloride, as was sodio formyl acetone (Method (1) for compound 3). Forty-four grams (0.36 mol) of the salt in 200 ml absolute EtOH and 20 ml 2,2-dimethoxypropane was allowed to react with 30 g (0.37 mol) of the amine hydrochloride. Work-up as for 3 (no distillation) gave 29.8 g (65%) brown syrup which was a 4:3 mixture of 4a and 4b. Nmr of 4a in neat mixture δ 1.57 (s, 3, vinyl CH_3), 1.80 (s, 3, $C\underline{H}_3CO$-), 2.75 (s, 6, $C\underline{H}_3N$-), 6.90 (s, 1, vinyl H); for 4b in the mixture δ 0.80 (t, 3, J = 7 Hz, $C\underline{H}_3CH_2CO$-), 2.55 (s, 6, $C\underline{H}_3N$), 2.55 (q, 2, J = 7 Hz, $CH_3C\underline{H}_2CO$), 4.63 (d, 1, J = 13 Hz, α-vinyl H), 7.10 (d, 1, J = 13 Hz, β-vinyl H).

Cooling this mixture to -10°, filtration, and two recrystallizations of the solid from ether gave 10.3 g (22%overall) of 98 mole % 4a, as white needles, mp 41-42° [lit. mp 55°,[25] 40°[71]]. Ir (CCl_4) 1663 (s, C=O *s-cis*), 1641 (s, C=O, *s-trans*),[23a] 1600 cm^{-1} (vs, C=C); nmr (CCl_4) δ 1.79, 1.90, 2.90, 6.95; assignments in same sequence as for 4a in mixture with 4b.

4-Diethylamino-3-(2-propyl)-3-buten-2-one (6a) and trans-1-diethylamino-5-methyl-1-hexen-3-one (6b). The enamine *trans*-1-diethylamino-3-methyl-1-butene (5) was prepared essentially as described by Stork, *et al.*, for related compounds.[56] Addition of 86 ml (0.8 mol) isovaleraldehyde to a stirring suspension of 41 g K_2CO_3 in 212 ml (2.0 mol) diethylamine at 5° produced after filtration and exhaustive vacuum stripping (32°/30 mm), 87.4 g (77%) of a very pale green liquid, ~97 mole % **5** by nmr. Nmr (neat) δ 0.67 (d, J = 7 Hz, $(C\underline{H}_3)_2CH$-), 0.77 (t, J = 7 Hz, $C\underline{H}_3CH_2N$-, overlaps δ 0.67, total both 12), δ 1.90 (multiplet, each line with slight shoulder, 1, J_{appar} = 7, ~0.7 Hz, $Me_2C\underline{H}$), 2.62 (q, 4, J = 7 Hz, $CH_3C\underline{H}_2N$-), 3.75 (dd, 1, J = 14 and 7 Hz, -C$\underline{H}$=CH–N-), 5.50 (dd, 1, J = 14 and ~0.7 Hz, -CH=C$\underline{H}$–N-).

This enamine **5** was acetylated in the way described above for 1-diethylamino cyclopentene. Addition 22.1 ml (0.31 mol) acetyl chloride in 80 ml $CHCl_3$ to 42.5 g (0.30 mol) **5** and 45 ml (0.33 mol) triethylamine in 300 ml $CHCl_3$ produced 40.8 (99%) triethylammonium chloride and 53.5 g (97%) crude 3:1 mixture of **6a** and **6b**. Only the olefinic protons are cleanly separated in the nmr spectrum of the neat mixture. For **6a** δ 6.92 (s, vinyl H); for **6b** δ 4.96 (d, 1, J = 13 Hz, α-vinyl H), 7.38 (d, 1, J = 13 Hz, β-vinyl H).

Distillation of the mixture from a little K_2CO_3 using a Claisen head as a "column" gave a mid-cut of 23.4 g (42% from the enamine) ~95 mole % **6a**, bp 93-101° (1.7 mm) as a yellow liquid. Ir (CCl_4) 1636 (s, C=O), 1597 cm^{-1} (vs, C=C); nmr (neat) δ ~0.9 (complex signal, 12, $(C\underline{H}_3)_2CH$ and $C\underline{H}_3CH_2N$), 1.82 (s, 3, $C\underline{H}_3CO$), 2.57 (septet, 1, J = 7 Hz, $(CH_3)_2C\underline{H}$), 3.04 (q, 4, J = 7 Hz, $CH_3C\underline{H}_2N$-), 6.80 (s, 1, vinyl H).

The compound **6a** was concentrated in the lower boiling fractions from the distillation; the isomeric **6b** prevailed in the higher boiling ones.

Reaction of Acetoacetaldehyde Dimethyl Acetal (7) with Aliphatic Amines. The starting material, Eastman 4,4-dimethoxy-2-butanone (7), was a yellow liquid, ~ 95 mole % by nmr, used without further purification. Nmr (neat) δ 1.78 (s, 3, $C\underline{H}_3CO$), 2.37 (d, 2, J = 6 Hz, $CO-C\underline{H}_2$), 2.93 (s, 6, $C\underline{H}_3-O$), 4.39 (t, 1, J = 6 Hz, $C\underline{H}(OMe)_2$). Since ample quantitites of tertiary aminobutenones were already in hand when the preparations described below were done, the products of reaction of 7 with secondary amines were not purified.

Reaction with t-butylamine. Twenty-one grams (0.15 mol) 7 was refluxed 48 hours with 22 g (0.30 mol) of the amine, whereupon the nmr spectrum of the reaction mixture showed no acetal 7, but ~ 4:1 mixture of *cis*:*trans* 4-(t-butylamino)-3-buten-2-one (9) (only vinyl protons reported); $\delta_{\underline{cis}}$ 4.58 (d, 1, J = 7 Hz, α-vinyl H), 6.50 (dd somewhat broadened, 1, J = 13 and 7 Hz, β-vinyl H); $\delta_{\underline{trans}}$ 4.92 (d, 1, J = 13 Hz, α-vinyl H), 7.20 (d, 1, J = 13 Hz, β-vinyl H).

After stripping methanol and excess amine, filtration gave 15.1 g (72%) crude 9 as dirty yellow crystals. In CCl_4, this material was ~ 95% *cis*-9; nmr (CCl_4) δ 1.15 (s, 9, $(C\underline{H}_3)_3C-N-$), 1.78 (s, 3, $C\underline{H}_3CO$), 4.71 (d, 1, J = 13 Hz, α-vinyl H), 6.53 (dd, 1, J = 13 and 7 Hz, β-vinyl H), 10.8 (broad and unresolved, 1, N-H---O). Only the vinyl protons of *trans*-9 could be separately seen in CCl_4: δ 5.00 (d, 1, J = 13 Hz, α-vinyl H), 7.14 (d, 1, J = 13 Hz, β-vinyl H).

Two recrystallizations of the crude 9 from EtOAc gave 8.5 g (40%) nearly white needles, mp 50-51°. The nmr spectrum of this material in ethanol (only β-vinyl protons reported) showed ~ 5:2 *cis*:*trans*-9, $\delta_{\underline{cis}}$ 6.53 (somewhat broadened dd, J = 13 and 7 Hz), $\delta_{\underline{trans}}$ 7.35 (considerably broadened doublet, J = 13 Hz).

Reaction with diethylamine. Refluxing 13.2 g (0.1 mol) 7 with 23 ml (0.22 mol) of the amine yielded after evaporation of the reaction mixture at 75°/40 mm 12.9 g (91%) brownish liquid whose nmr spectrum showed it to be > 95 mol % *trans*-4-diethylamino-3-buten-2-one. Nmr (neat) δ 0.80 (t, 6, J = 7 Hz, $C\underline{H}_3CN_2H$-), 1.72 (s, 3, $C\underline{H}_3CO$-), 2.91 (q, 4, J = 7 Hz, $CH_3C\underline{H}_2N$-), 4.72 (d, 1, J = 13 Hz, α-vinyl H), 7.10 (d, 1, J = 13 Hz, β-vinyl H).

Reaction with pyrrolidine. Following essentially the procedure for diethylamine, using 13.2 g (0.1 mol) 7 and 17 ml (0.2 mol) of the amine, 12.2 g (88%) *trans*-4-N-pyrrolidino-3-buten-2-one (14) was obtained as a brown oil ~ 95 mole % pure. Nmr ($CHCl_3$)δ 1.97 (m, β-pyrrolidino H's), 2.10 (s, $C\underline{H}_3CO$, overlaps δ 1.97, total both 7), 3.33 (broad distorted multiplet, 4, α-amino H's), 5.05 (d, 1, J = 13 Hz, α-vinyl H), 7.67 (d, 1, J = 13 Hz, β-vinyl H). The same nmr spectrum was shown by material obtained by the reaction of the amine with $CH_3COCH{=}CHCl/CH_3CO{-}CH_2{-}CHCl_2$, performed in the same way as that used to make $Me_2N{-}CH{=}CH{-}COMe$ (3) by method (2) above.

Reaction of 4-methoxy-3-buten-2-one (8) with aniline. The starting material 8 was made by reaction of the acetal 7 with sodium methoxide with continuous distillation of methanol exactly as described by Royals and Brannock[63]; bp 173-175° (745 mm), 75-77° (25 mm) [lit. bp 52-53° (4-5 mm),[63] 172° ("normal pressure")[72]].

Ten grams (0.10 mol) of the vinylogous ester 8 was allowed to stand for 20 hours with 9.3 ml (0.10 mol) aniline at 22°. Filtration gave 13.6 g (84%) of a pale yellow solid. This material showed mp's with 2-3° ranges from 84-105° depending on the rate of heating and whether the sample had been previously melted. Material recrystallized from absolute ethanol gave some liquid at 53-56°, the bulk melting 95-96°, and all refreezing to *white* solid. The existence of two slowly interconverting solid forms of 4-anilino-3-buten-2-one has been noted.[41]

The nature of this polymorphism together with some incomplete nmr data on this compound is more fully discussed in Proposition I, attached to this thesis.

4-N-piperidino-3-penten-2-one (11). In a typical run, 30 ml (0.30 mol) acetylacetone (10) and 40 ml (0.40 mol) piperidine were refluxed in 300 ml toluene under a graduated water separator until water generation ceased (~ 5.1 ml, 95%). The orange-red solution was then stripped on a rotary evaporator, chilled in ice, and 31 g (62%) crude 14 filtered off, large yellow-orange crystals. Repeated recrystallization from benzene/ligroin and ether gave 8-10 g (16-20%) 14 as snow-white needles, mp 47-48°. Undoubtedly a cleansing distillation would have afforded much higher yields of colorless material. Ir (CCl_4) 1650 (s, C=O), 1547 cm^{-1} (s, C=C); ir (CH_2Cl_2) 1633, 1544 cm^{-1}; ir ($CHCl_3$) 1625, 1537 cm^{-1}. Nmr ($CHCl_3$) δ 1.59 (broad multiplet, 6, β- and γ-piperidino H's), 2.06 (s, 3, $C\underline{H}_3CO$-), 2.50 (s, 3, $C\underline{H}_3C{=}C$-), 3.35 (broad multiplet, 4, α-piperidino H's), 5.24 (s, 1, vinyl H). White material discolored slightly over 3 years at 0° under N_2.

4-Dimethylamino-3-penten-2-one (12). My procedure is similar to one reported[33] except for the use of the dehydrating solvent 2,2-dimethoxypropane (DMP). In a thick-walled Erlenmeyer flask, 17 ml (0.26 mol) dimethylamine was added to a cooled solution of 25 ml (0.25 mol) 10 in 40 ml DMP containing 5 drops conc. HCl, The vessel was stoppered tightly and placed in an oil bath held at 60-70° for 36 hours. After cooling and vacuum stripping, the resulting orange syrup was chilled, and 29.9 g (94%) crude 12, yellow-orange crystals, was filtered off. Recrystallization from benzene/ligroin and ether gave 12.5 g (39%) white needles. Mp 47-48° [lit.[33] mp 46-47°]; nmr ($CHCl_3$) δ 2.00 (s, 3, $C\underline{H}_3CO$-), 2.45 (s, 3, $C\underline{H}_3C{=}C$-), 2.95 (s, 6, $C\underline{H}_3N$-), 5.00 (s, 1, vinyl H). Storability like that of 11.

4-N-Pyrrolidino-3-penten-2-one (13).

Method (1). This compound was obtained from the reaction of 10 with pyrrolidine in ethyl acetate exactly as described by Leonard and Adamik.[34] White needles; mp 114.5-116° [lit.[34] mp 115-116°]; ir (CCl_4) 1626 (s, C=O), 1535 cm^{-1} (s, C=C) [lit.[34] 1623, 1535 cm^{-1}]; nmr ($CHCl_3$) δ 1.93 (multiplet, β-amino H's), 2.01 (s, $C\underline{H}_3CO$-, overlaps δ 1.93, total both 7), 2.48 (s, 3, $C\underline{H}_3C{=}C$-), 3.30 (distorted triplet, 4, J ~ 7Hz, α-amino H's), 4.93 (s, 1, vinyl H). No discoloration on storage several months over KOH/H_2SO_4/paraffin shavings.

Method (2). A mixture of cis- and trans-4-chloro-3-pent-2-one was made in poor yield as follows (cis means Cl- and Ac- cis): One hundred ml (1.0 mol) 10 and 35 ml (0.4 mol) PCl_3 in 170 ml $CHCl_3$ were refluxed for 5 hours; brown solid appeared. The mixture was cooled and poured over ~100 g cracked ice. The layers were separated, and the aqueous phase extracted with 4-50 ml portions $CHCl_3$. The combined organic extracts were washed with 3-100 ml portions 2 N NaOH and then 100 ml water. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated at 41°/50 mm, leaving 18 g (15%) brown liquid with a minty odor. Nmr assay showed this material to be ~3:7 mixture of cis- and trans-4-chloro-3-penten-2-one. Nmr (neat) δ_{cis} 1.76 (s, 3, CH_3CO-), 1.87 (d, 3, J = 2 Hz, $CH_3C{=}C$-), 5.9 (broad singlet, 1, vinyl H); δ_{trans} 1.76 (s, 3, CH_3CO-), 2.11 (d, 3, J = 1 Hz, $CH_3C{=}C$-), 6.05 (broad singlet, 1, vinyl H).

To a cooled solution of 11.2 g (95 mmol) of the above mixed chloroketones in 50 ml ether was added dropwise 21 ml (250 mmol) pyrrolidine with stirring. After stirring at 25° for 3 hours, the solution was filtered, the solid washed well with ether, and the ether solution evaporated to give a brownish sludge with yellow crystals in it. This mass was dissolved completely in ~25 ml $CHCl_3$. The nmr spectrum of this solution was identical to that of authentic 13 prepared by Method (1) except for trace impurities; no new peaks appeared on addition of Method (1) material. No unreacted chloroketone was detected.

N,N-Diethyl 3-N-pyrrolidino-2-butenamide (?) (15). The procedure was similar to that for 11. A mixture of 23.5 g (0.15 mol) re-distilled N,N-diethylacetoacetamide (bp 132-133° (24 mm)) and 20 ml (0.24 mol) pyrrolidine was refluxed in 90 ml benzene. During 1 hour, 3.2 ml (118%) water separated. The solution was stripped, and the residual yellow-orange oil was distilled in a semi-micro apparatus to give a middle cut of 25.8 g (82%) 15 as a yellow-orange liquid. Bp 126-139° (0.15 mm); ir (CCl_4) 1617 (vs, C=O), 1564 cm^{-1} (vs, C=C); nmr (CCl_4) δ 0.91 (t, 6, J = 7 Hz, $C\underline{H}_3CH_2N$-), 1.80 (broad multiplet, 4, β-pyrrolidino H's), 2.25 (s, 3, $C\underline{H}_3C{=}C$-), ~3.1 (broad complex signal, 8, all α-amino H's), 4.39 (s, 1, vinyl H). This material darkens on storage; fresh pale green condensate discolors on contact with silicone grease.

Trans-1-(3-(N-piperidino)-propenoyl)-piperidine (16). The conversion of acetylenedicarboxylic acid monopotassium salt to *trans*-3-chloropropenoic acid[73] was accomplished without isolation of the intermediate propiolic acid.[74]

A suspension of 170 g (1.12 mol) of the salt in 300 ml water was heated on a steam bath until CO_2 evolution ceased (ca. 2 hours). After vacuum stripping the yellow solution, 146 g damp yellow solid remained (potassium propiolate). To this solid, 350 ml conc HCl was added with cooling. The mixture after 2 hours reflux and subsequent cooling was a brownish solution with a gelatinous solid plus white leaflets in it. This was diluted with ~400 ml water to dissolve all the solids and extracted with 6-100 ml portions CH_2Cl_2.

The extracts were dried ($MgSO_4$) and stripped; the residue on recrystallization from 65 ml 1:2 conc HCl:H_2O gave 48 g (40%) trans-3-chloropropenoic acid as brown stained thin flakes, anhydrous by nmr after air dry. Nmr (CCl_4) δ 6.25 (d, 1, J = 14 Hz, α-vinyl H), 7.50 (d, 1, J = 14 Hz, β-vinyl H), 12.50 (s, 1, -COOH) [lit.[45] δ 6.22, 7.48 with J = 13.2 Hz].

The conversion of this acid to the vinylogous urea **16** is described in the manuscript "Paper II" attached to this thesis.

Cis and trans-3-chloro-2-butenoyl chloride (**18**). The acids **17** were made essentially as described by Jones, et al,[66] except that a smaller excess of PCl_5 was used. In my hands, the intermediate esters of **17** were harder to hydrolyze than one would infer from the procedure described.[66]

To 200 g (0.96 mol) PCl_5 stirring in 100 ml benzene at 0-5° was added over 1 hour 91 g (0.70 mol) ethyl acetoacetate. After stirring at 0-15° for 18 hours, 250 ml water was added slowly, keeping the pot temperature below 45°. After 18 hours stirring at 23°, the layers were separated. Extraction of the aqueous layer with CH_2Cl_2, drying of extracts, stripping, and cooling afforded only 1.42 g of solid; the filtrate from this work-up (~ 5 g) was added to the benzene layer. The stripped benzene layer's nmr spectrum showed only the ethyl esters of **17** (no -COOH signal) and a little of the starting ester. Accordingly, this material (~ 70 g, contained some benzene) was refluxed with vigorous stirring with 350 ml constant boiling HCl for 21 hours. The layers were again separated;

the lower one, a brownish oil, solidified on seeding. The aqueous layer was extracted with CH_2Cl_2 (5 × 50 ml), the extracts stripped, and the residue cooled and seeded. Filtration and re-work of the mother liquors ultimately gave a total of 28.7 g (34%) of the stereomeric acids 17 as a light yellow solid, >95 mole % pure by nmr with a trans:cis ratio of 2:1. In the nmr spectrum of the mixture, the signals of vinyl protons partially overlap, and there was a single carboxylate H absorption whose intensity was equal to that of the sum of vinyl H signals (i.e., the mixture was dry). Nmr (CCl_4) δ_{cis} 2.23 (d, J = 1.4 Hz, methyl), 5.91 (q, J = 1.4 Hz, vinyl H), 12.33 (s, COOH); δ_{trans} 2.75 (d, J = 1.7 Hz, methyl), 5.99 (q, J = 1.7 Hz, vinyl H), 12.33 (s, -COOH).

A mixture of 27.8 g (0.23 mol) 17 and 28 ml (0.39 mol) $SOCl_2$ was refluxed until the pot temperature ceased to rise (~ 45 min, T_{max} = 108°). Vacuum distillation in a semimicro apparatus, overdriving the condenser slightly, gave 25.7 g (80%) of a colorless liquid, bp 49-65° (14-16 mm), which was a 4:3 mixture of trans:cis acid chlorides 18 [lit.[75] bp_{trans} 135-136° (760 mm)]. This material contained a trace of $SOCl_2$ (very weak band at 1234 cm^{-1} in CCl_4 solution). Hydrolysis with cold water of liquid collected in a trap after the distillate receiver gave 3.43 g white solid which was 95:5 trans:cis mixture of the acids 17, mp 55-58° [lit.[66] mp_{trans} 60.3-60.6°]. Thus the yield of 18 from unrecovered 17 was 92%. Assuming most of the loss was of the more volatile trans-18, the conversion of the mixed 17's went without isomerization. Since the stereomeric mixture of 18 collected was richer in the *less* stable *cis* isomer[45, 67] than the starting acids 17, this assumption is reasonable. Ir(CCl_4) 1780, 1759 (s, C=O's), 1603 cm^{-1} (s, C=C); nmr (neat) δ_{cis} 2.10 (d, J = 1 Hz, methyl), 6.17 (q, J = 1 Hz, vinyl H), δ_{trans} 2.26 (d, J = 1 Hz, methyl), 6.20 (q, J = 1 Hz, vinyl H). The vinyl H absorptions overlap but show 8 lines total for both stereomers.

Reaction of acid chlorides 18 with diethylamine. This reaction was run as a preliminary test for the preparation of 19 below.

To a solution of 2.8 g (20 mmol) 18 in 80 ml ether 2.9 g (40 mmol) amine was added dropwise at 0-5° with stirring. After 3 hours, 2.1 g (19 mmol) diethylammonium chloride was filtered off, and the filtrate stripped to yield 3.2 g (91%) yellow liquid whose nmr spectrum was consistent with a 4:3 mixture of *trans*:*cis*-$CH_3-C(Cl)=CH-CO-NEt_2$, the same stereomeric ratio as for 18. There was only one kind of N-ethyl group and one multiplet for both vinyl protons, but the vinyl methyls in the two stereomers were clearly distinct. Nmr (neat) δ 0.92 (t, J = 7 Hz, $C\underline{H}_3CH_2N$-), 1.97 (d, J = 1 Hz, vinyl methyl in *cis*-isomer), 2.15 (d, J = 1 Hz, vinyl methyl in *trans*-isomer), 3.13 (q, J = 7 Hz, $CH_3C\underline{H}_2N$-), 6.12 (m, vinyl H in both isomers). This mixture of β-chloroamides on standing in a solution of 10 ml (large excess) diethylamine in 50 ml ether at 25° slowly deposited a small amount of white solid over several weeks.

1-(3-(N-piperidino)-2-butenoyl)-piperidine (19). As for the reaction of 18 with diethylamine, 25 ml (250 mmol) piperidine in 20 ml ether was added to 4.2 g (30 mmol) 18 in 100 ml ether, after which the mixture was refluxed for 4 hours. The nmr spectrum of the filtered and stripped filtrate (5.7 g) showed two multiplets at δ 6.0 and 6.2, a less intense singlet at δ 4.65, and two broad α-piperidino proton absorptions at δ 3.25 (more intense) and δ 2.9. Inferring that this oil was a mixture of β-chloroamides with the desired compound 19, the oil was refluxed with 15 ml (150 mmol) piperidine in 100 ml benzene for 17 hours. After filtration and stripping of solvent and excess amine, 5.9 g (83%) of an orange-brown oil was obtained whose nmr spectrum was consistent with that expected for 19 (one isomer). Nmr (CCl_4) δ 1.47 (broad, 12, all β- and γ-amino H's), 2.08 (s, 3, methyl), 2.97 and 3.30 (two broad distorted but distinct envelopes, 4 each, α-amino H's), 4.79 (s, 1, vinyl H). Which α-piperidino proton envelope belongs to which of the two different piperidino groups is not clear. The spectrum of the mixture of 19 with the intermediate chloroamides (see above) suggests that the higher field signal belongs to the vinyl piperidino group.

Since the purpose in preparing 19 was to show that it is *not* the product arising from reaction of $CH_3CO\text{-}CH{=}CCl_2$ with piperidine (see Chapter II), it was not further purified.

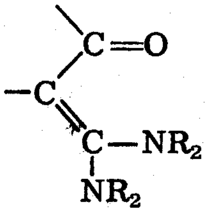
CHAPTER II

Ethynylogous and Vinylidenologous Amides. The Reaction of Activated Vinylidene Chlorides with Secondary Amines

Introduction

Brief mention of the observation that stimulated my interest in the subject of this chapter was made in the general introduction to this thesis. A fuller explanation is given below.

Initial studies on cobalt(II) chloride complexes (part II of this thesis) with the simple vinylogous amides described in the preceding chapter indicated that the latter were behaving as monodentate ligands. In the belief that a compound with the functionality



would likely be bidentate, I decided to make such a compound.

The reaction of β,β-dichlorovinyl ketones (vinylidenologous acid chlorides) with amines to produce compounds with the desired functionality had been reported.[39, 76] Accordingly, the easily prepared ketone $CH_3CO{-}CH{=}CCl_2$ was allowed to react with an excess (5 moles) of diethylamine in ether. Besides two moles of amine hydrochloride, there was obtained a liquid whose nmr showed one diethylamino moiety, a $C\underline{H}_3{-}C{=}$ methyl and no other proton resonance. The infrared spectrum of this compound showed a very strong band at 2162 cm^{-1} and a strong amide-range carbonyl absorption at 1636 cm^{-1}. The product was thus tentatively formulated as $CH_3CO{-}C{\equiv}C{-}NEt_2$.

Ethynylogous amides had been only recently reported[77, 78] at the time of this discovery, having been obtained by more difficult procedures. On the basis of the above novel result, an extended investigation of the reaction of activated vinylidene chlorides (AVDC's) having α-hydrogen, $CL_2C{=}CH{-}L$ (L = carbonyl function of -CN) was undertaken.

Syntheses of Activated Vinylidene Chlorides

For these studies, it was of course necessary to find suitable routes to the AVDC's. Since such compounds have been much less investigated[79] than those with a single activated halogen, the development of satisfactory preparations was sometimes quite challenging.

Ketones. Four compounds of structure $RCO{-}CH{=}CCl_2$ were made with R = CH_3 (**20**), C_6H_5 (**21a**), $ClCH_2$ (**22a**), and $(CH_3)_2CH$ (**23**); the latter two were intended only as prospective intermediates for $Cl_2C{=}CHCOOH$. All the ketones were made from vinylidene chloride (**24**) by Friedel-Crafts/Darzens acylation.[39, 80, 81] Since the olefin **24** is now inexpensive, the reaction was done by adding aluminum chloride to a mixture of $RCOCl/CH_2{=}CCl_2$ (large excess)/CH_2Cl_2, rather than by pre-forming the $RCOCl$-$AlCl_3$ complex and then adding **24**, the usual procedure.[39, 81] Use of CH_2Cl_2 rather than CCl_4[81] or excess chloride[82] as the solvent/diluent facilitated stirring. It was found desirable to have $AlCl_3$ as the limiting reagent and to add it at

~ -15° to minimize tarring; uncomplexed $AlCl_3$ rapidly tars **24**.

In all the acylations, very little HCl is evolved during the reaction. Yet after quenching the reaction mixture with ice, even undistilled crudes were all (**20**) to part (**21**-**23**) the desired *unsaturated* ketones admixed with the corresponding saturated β,β,β-trichloroketones. Thus even cold water is a sufficiently good base to cause dehydrochlorination in these compounds:

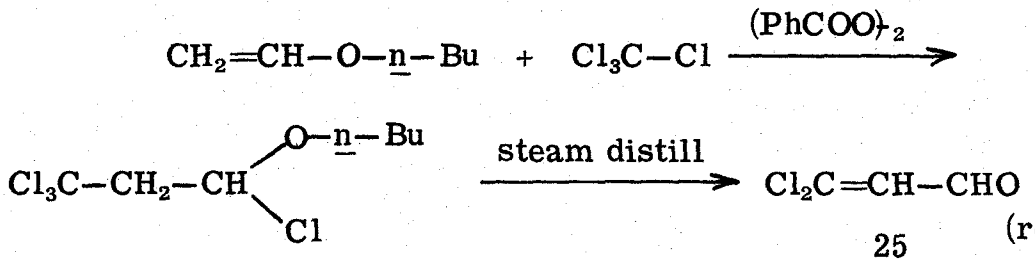
$$\begin{gathered} Cl_3C{-}CH_2{-}COR + H_2O \rightarrow \\ Cl_2C{=}CH{-}COR + H_3O^+Cl^- \end{gathered}$$

The very facile β-elimination of HCl to produce **20** has been attributed to the ease of its attaining planarity.[81] Since in my work, the ketones **21a,b** and **22a,b** were to be reacted with bases, no attempt was made to convert completely **21b** to **21a** and **22b** to **22a**.

The ketone **20** is unstable when dry[83,84] unless scrupulously free from HCl, undergoing an auto-catalyzed decomposition.[83] The other ketones **21a**-**23** are stable even admixed with their saturated adducts, which continuously evolve HCl.

Aldehydes. The compounds $Cl_2C{=}CH{-}CHO$ (**25**) and its α-methyl homolog (**26**) were made by reported procedures[85a,b, 86] summarized below:

For **25**:



$CH_2{=}CH{-}O{-}\underline{n}{-}Bu + Cl_3C{-}Cl \xrightarrow{(PhCOO)_2}$

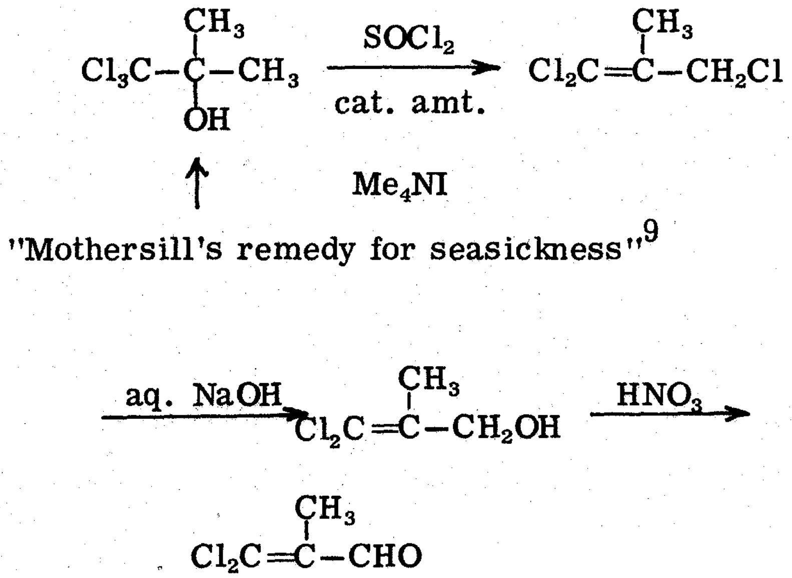
$Cl_3C{-}CH_2{-}CH(O{-}\underline{n}{-}Bu)Cl \xrightarrow{\text{steam distill}} Cl_2C{=}CH{-}CHO$

25

(ref. 85a,b)

(purified via
bisulfite adduct)

For 26:



$Cl_3C{-}C(CH_3)(OH){-}CH_3 \xrightarrow[\text{cat. amt.}]{SOCl_2} Cl_2C{=}C(CH_3){-}CH_2Cl$

Me_4NI

$\uparrow$

"Mothersill's remedy for seasickness"[9]

(ref. 86)

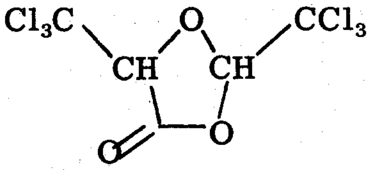
$\xrightarrow{\text{aq. NaOH}} Cl_2C{=}C(CH_3){-}CH_2OH \xrightarrow{HNO_3}$

$Cl_2C{=}C(CH_3){-}CHO$

26

No noteworthy observations different from those of the original workers[85,86] were made. The aldehyde 26 was made only for the reasons stated in Paper II, appended hereto.

Functional Derivatives of 3,3-Dichloropropenoic Acid (27). Although the acid 27 has been known for 95 years,[87] satisfactory preparations for large quantities have not appeared in the literature.

The compound **27** has been made in several ways, *inter alia* by (1) reduction of chloralide,[87]  , in unstated yield, the process also giving *trans*-chloropropenoic acid; (2) by addition of HCl to $ClC{\equiv}C{-}COOH$[88] (low overall yield); and (3) by hydrolysis of $Cl_2C{=}CH{-}CCl_3$[89] (halide in only 25% yield from Cl_3CCHO and $Ph_3P{=}CCl_2$). Oxidation of the aldehyde **25** to **27** by Ag_2O has been done,[85b] but this is hardly a preparative scale reaction.

A number of attempts to make functional derivatives of **27** in one step by Darzens acylation of **24** with a reagent already containing a carbon moiety in the carboxyl oxidation state failed completely or gave very poor results. Attempted acylation with phosgene by adding **24** slowly at -20° to excess pre-formed $COCl_2$-$AlCl_3$ complex in CH_2Cl_2 gave only heavy tarring. Similar reaction of **24** with oxalyl chloride under conditions coincidentally nearly identical to those of Levas[90] (not known at the time) gave similar results, i.e. a low yield of Cl_3CCH_2COCl. I obtained a small amount of $Cl_2C{=}CH{-}COCl$ (ir same as authentic material) by repeated distillation of the mixture containing the saturated acid chloride, but the method is not preparatively useful. My hope for this method lay in the fact that oxalyl chloride often acylates aromatics in good yield with loss of CO.[91] The obtaining of only poor yields of any distillable product from Darzens acylation of **24** with the more reactive acyl halides (e.g., *p*-nitrobenzoyl, dichloroacetyl) has been noted.[84]

Attempted acylation with EtOCOCl/$AlCl_3$ led only to mild explosions (often after a regrettably long induction period!), due no doubt to decarboxylation of EtOCOCl.[92] The milder catalyst $SnCl_4$ did not decarboxylate EtOCOCl but also gave no acylation product with 24. Diethylcarbamyl chloride with $AlCl_3$ simply failed to react with 24; only starting material was recovered even after prolonged refluxing at 60-70°. The fact that this reaction mixture darkened only slightly shows that the $AlCl_3$ was complexed with the acylating reagent. Similarly, cyanogen bromide with $AlCl_3$ in CH_2Cl_2 or in nitrobenzene or nitromethane failed to give material showing a $C\equiv N$ absorption in the ir on reaction with 24 under conditions where some olefins do give nitriles.[93] This result does not necessarily mean that cyanogen chloride would fail, but the negative results with BrCN dissuaded me from trying the dangerous chloride (bp 15°), not at the time available in cylinders.

Taken together, the above attempts at Darzens acylation indicate the olefin 24 gives good results only with acyl halides of intermediate reactivity.[94] With very reactive ones, the sensitivity of 24 to polymerization leads to extensive tarring [81,84]; with relatively unreactive ones, the electron-poor olefins 24 fails to react (cf. the general resistance of aryl chlorides to electrophilic attack on the ring compared to the corresponding hydrocarbon).

One last method that failed to give the desired result was attempted Baeyer-Villiger oxidation of the ketone 23:

$$\underset{\textbf{23}}{Cl_2C{=}CH{-}CO{-}\underline{i}{-}Pr} \quad \xrightarrow[]{\text{peracid}}\!\!\!\!\!\!\!\!\!\!\!\!\times \qquad Cl_2C{=}CH{-}COO{-}\underline{i}{-}Pr$$

Using the usual conditions for this reaction[95] with either peracetic or m-chloroperbenzoic acid gave at most small amounts of material showing the $-CO-O-C\underline{H}(CH_3)_2$ group by nmr (septet at ~ 4 δ[16, 51]) in a complex mixture.

None of the above unproductive schemes will be mentioned further in this thesis.

Two synthetically useful routes to the desired derivatives of the acid 27 were developed, viz. (1) the haloform reaction on a mixture of the ketones 22a, b, and (2) manipulations of the nitrile $Cl_2C{=}CH{-}CN$ which can be made in three steps from chloral in only moderate overall yield but on a large scale.

With the methyl ketone 20 in hand, the haloform reaction is an obvious route to the acid 27. In practice however, it presented certain difficulties. Using commercial chlorine bleach, "Clorox" or equivalent (5% NaOCl, ~ 0.7 M), required a large solution volume (~ 350 ml aqueous hypochlorite for 0.1 mole ketone 20) and the reaction was slow below ~ 10°. At higher temperatures the product acid 27 undergoes decomposition in the basic medium to give explosive chloroacetylene[96] by decarboxylative dehydrochlorination. The use of dioxane as a co-solvent[97] to make the reaction mixture homogeneous renders the acid 27 hard to separate since it does not crystallize well from this solvent and is appreciably volatile.[89] The use of a more concentrated hypochlorite solution[97] causes rapid decomposition of the ketone 20 itself to $HC\equiv C{-}Cl$ even in the cold. This reaction, analogous to the "acid" cleavage of acetoacetic esters, is general for β,β-dichlorovinyl carbonyl compounds.[39,98-100] By careful control of temperature and reaction duration (monitoring of $CHCl_3$: ketone 20 ratio in lower layer by nmr), yields of 30-40% of the acid 27 were obtained using 0.1-0.2 mole 20, lower yields on larger scale.

Since the slowest step in the haloform reaction is the introduction of the first α-halogen,[101] I thought that starting with the α-chloromethyl ketone 22a might permit a lower reaction temperature and reduce the reaction volume (only 2 moles of hypochlorite per mole of ketone 22a needed).

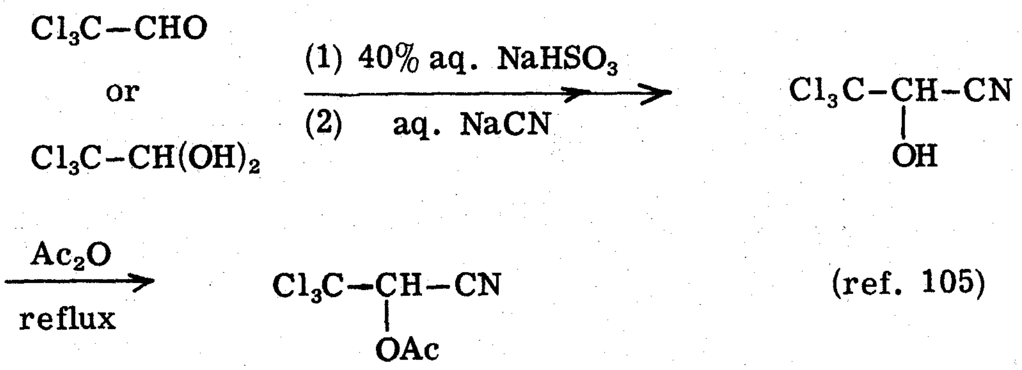
This idea proved productive. Darzens acylation of 24 gave the chloroketones 22a and b in 70-80% yield. The unsaturated ketone 22a could be frozen out of the mixture, but this was not necessary. The crude mixture of 22a and b gave a 65-75% yield of the acid 27 with 5% aqueous NaOCl. The yield and the absence of 22b in the organic layer of the mixture at the end of the reaction showed that both 22a and b were giving the desired product 27. The yield in this reaction decreased when more than ~ 0.2 mole of the mixed ketones 22a, b (reaction volume ~ 650 ml) was used per batch.

The acid 27 was readily converted to the acid chloride (28) by $SOCl_2$ and to its methyl ester (29) by Fischer esterification. The latter reaction required rather prolonged refluxing with ~ 10% H_2SO_4 in methanol for high conversion of 27 to 29.

The acid chloride 28 was easily converted to amides in good yield; in particular the unsubstituted amide (30) was obtained by reaction of 28 with cold aqueous ammonia.

The amide 30 was converted to the nitrile (31) in only fair yield by dehydration with $SOCl_2$ in benzene; this route to 31 requires three steps from the acid 27. Attempts to convert the acid 27 to the nitrile 31 in one step by use of $ClSO_2NCO$[103] failed completely. In my hands, attempts to prepare the oxime of the aldehyde 25 with the intention of dehydrating this derivative to the nitrile 31 failed when I could not isolate the oxime. After this route had been abandoned, a procedure for making 31 this way without isolating the unstable oxime of 25 was reported.[79]

Finally, recourse was had to the literature procedure for the nitrile,[104] starting with chloral (or its hydrate). This method was initially avoided because of the political difficulty in obtaining chloral (controlled drug) and the apparent need to work with HCN. When I found that the cyanohydrin could be made via the bisulfite compound, the following sequence was executed:



$$\begin{array}{c}\mathrm{Cl_3C{-}CHO}\\ \text{or}\\ \mathrm{Cl_3C{-}CH(OH)_2}\end{array} \xrightarrow[\text{(2) aq. NaCN}]{\text{(1) 40\% aq. NaHSO}_3} \mathrm{Cl_3C{-}\underset{\substack{|\\ OH}}{C}H{-}CN}$$

$$\xrightarrow[\text{reflux}]{\mathrm{Ac_2O}} \mathrm{Cl_3C{-}\underset{\substack{|\\ OAc}}{C}H{-}CN}$$

(ref. 105)

$$\xrightarrow{\text{Zn/boiling THF}} \quad Cl_2C{=}CH{-}CN \qquad \text{(ref. 104)}$$

31

Although this sequence gave only a moderate overall yield (~ 35%) of the nitrile, it could be run on scale that produced up to ~ 0.4 mole 31 per batch in the last step, and even larger amounts of the intermediates could be made in a single run.

Although adequate amounts of the other derivatives of the acid 27 were in hand when the nitrile 31 was made as above, some small-scale test runs were made to see if it might be suitable as a general intermediate for derivatives of 27. The nitrile 31 proved quite hard to hydrolyze, resisting reaction with refluxing 10 M H_2SO_4 or concentrated HCl. However, a good yield of the acid 27 was obtained by dissolving 31 in 90-98% H_2SO_4, and then diluting and refluxing the solution a few hours to hydrolyze the intermediate amide 30.

Overall, I conclude that the haloform sequence is good for the preparation of relatively small amounts of functional derivatives of the acid 27; those involving synthesis of the nitrile 31[79,104,106] are for larger amounts.

Reaction of Activated Vinylidene Chlorides (AVDC's) with Amines

Background. A number of reports on the reactions of AVDC's with a variety of nucleophiles have appeared, usually dealing with ketones[39,76,107] and more recently with nitriles.[79] Detailed information concerning reactions with secondary amines is largely confined to three theses.[84,99,108] The only previously known reaction yielding an acetylenic product without cleavage of the carbon chain from an

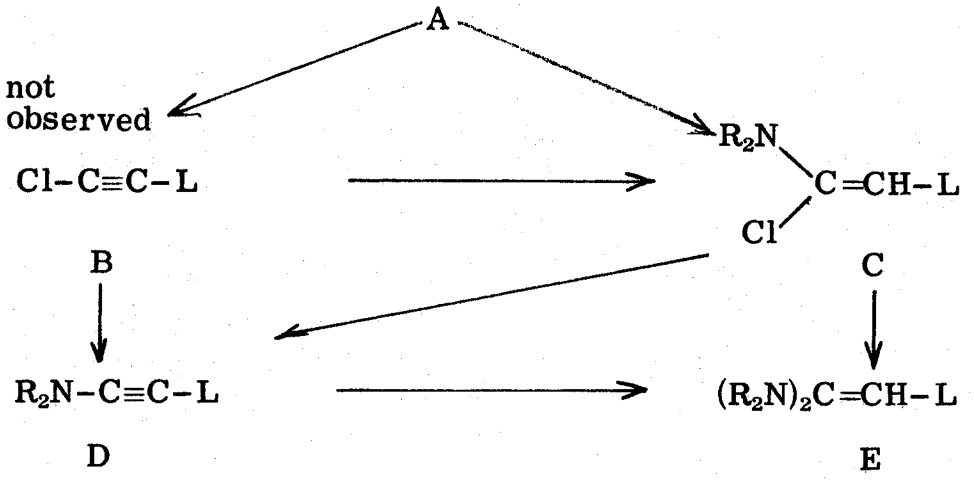
AVDC plus a nucleophile/base has been the production of a low yield of $\mathrm{PhCO{-}C{\equiv}C{-}Cl}$ from **21a** and hot aqueous KOH.[99] In the reaction of tritiated dimethylamine with **21a**, 98% of the activity was found in the by-product hydrochloride rather than in the β,β-bisaminoketone. The inference from this result was that there was no acetylenic intermediate,[39,99] the favored mechanism being two successive conjugate additions of the amine each followed by elimination to an olefin.[39]

My results discussed below contrast with the above. For every AVDC with α-hydrogen except the aldehyde **25**, I found evidence for generation of an acetylene with at least one secondary amine. For the ketone **20** and the nitrile **31**, the reaction was preparatively useful for making ethynylogous amides. These compounds have been previously made by three methods: (1) acylation of an ynamine generated *in situ*,[78] (2) bromination-dehydrobromination of the corresponding olefin (most general),[6] and (3) reaction of $\mathrm{R_2NH}$ with $\mathrm{Cl{-}C{\equiv}C{-}CN}$.[109] Of the three, the last method most closely resembles mine.

The reasonable reaction possibilities are summarized in the following two schemes:

Scheme I

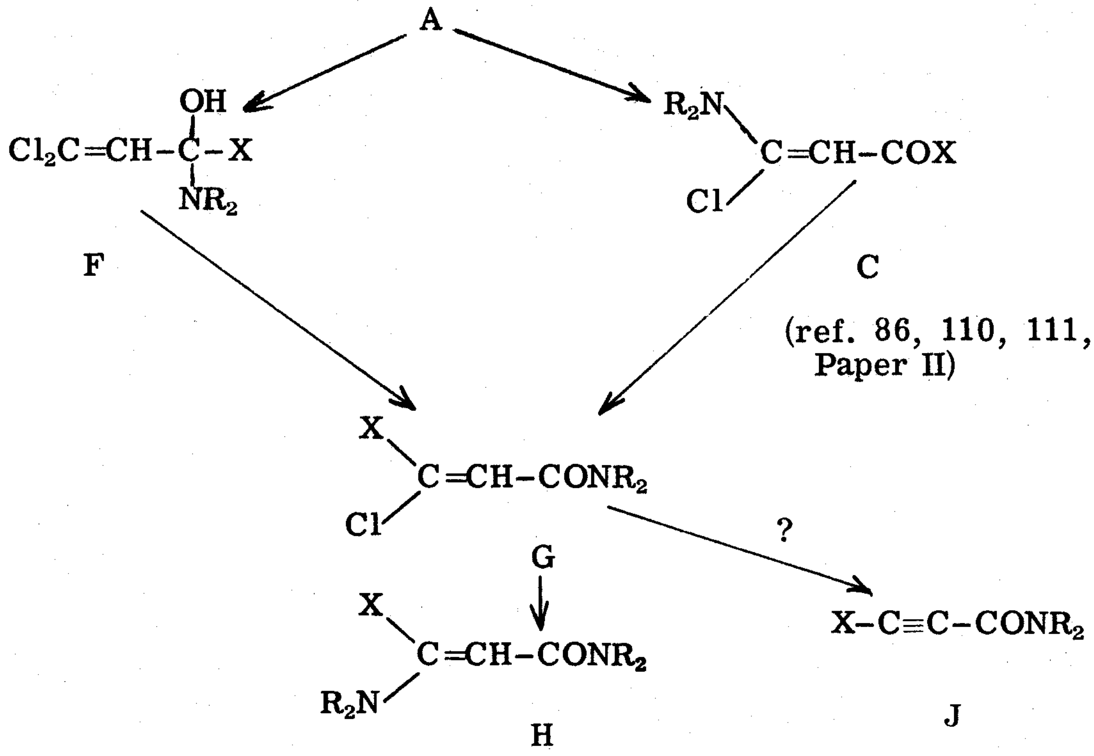
$R_2NH + Cl_2C{=}CH{-}L$ (L = carbonyl function or CN)



(The reactions A → C, B → D, and C → E probably involve conjugate addition-elimination.[39, 99])

Scheme II

$R_2NH + Cl_2C{=}CH{-}COX$ (X = H, alkyl or aryl, OR, NR'_2)



(ref. 86, 110, 111, and Paper II)

Results and Discussion. Following the discovery cited at the beginning of this chapter, the AVDC's were prepared and allowed to react with secondary amines under a variety of conditions.

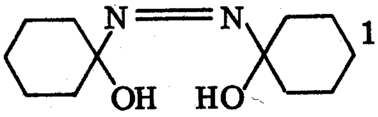
For the cases in which I assert that an acetylene was formed, this claim is based on the appearance of an ir absorption in the triple bond stretching region in either the reaction mixture and/or isolated product. That this acetylene was not of type B (Scheme I) is inferred from the failure of the acetylenic ir absorption to be accompanied by a relatively high carbonyl stretching absorption frequency; one would expect this absorption in type B species to be near that of the corresponding type A (confirmed for $Cl-C\equiv C-COCH_3$[99]), whereas all the type D species have this absorption at considerably lower frequency than the related type A ones.[6,78] The presence of a type E species in the cases where it was not isolated and purified was deduced from the appearance of a very low frequency C=O band and a very strong C=C absorption and/or a high field olefinic proton resonance ($\delta < 4.8$). This was typically found for all definitely identified type E species (see also Chapter III).

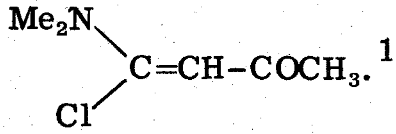
The aldehyde **25** was unique among the AVDC's with α-hydrogen in that at most only a small amount of D was detected on reaction with piperidine or diethylamine. This indicates either very rapid conversion of C → D or pronounced preference for the reaction C → E. Ethynylogous formamides are by far the least stable and most reactive of the known type D species.[6] Compound **25** was also the only AVDC that definitely formed some type H product (Scheme II);

this is discussed fully in Paper II, attached. Since the conversion C → G is inhibited by excess base, a route through F is more probable.

The reactions of the ketone 20 were the ones most thoroughly studied since the starting material was readily made in large quantities. Reaction of 20 with excess diethylamine in ether proceeded to the D species, $Et_2N-C{\equiv}C-COCH_3$ (32) and stopped, regardless of the order of addition. When 32 was allowed to stand 24 hours with excess Et_2NH, neat or in benzene, no type E was obtained. A little type E was formed from 20 plus Et_2NH in benzene or carbon tetrachloride, but this must come from C → E.

That 32 is not the isomeric acetylene $CH_3-C{\equiv}C-CONEt_2$ (type J) was shown by the facts that hydrogenation yielded $Et_2N-CH{=}CH-COCH_3$ (nmr) as the only olefinic product, and that authentic G reacted only sluggishly with Et_2NH at all and yielded no type J product (Chapter I).

An attempt to reduce 32 with diimide generated by decomposition of [112] gave no reduction product. The inability of HN=NH to hydrogenate highly polar carbon-carbon multiple bonds has been noted.[113]

The intermediate C was quite elusive. In efforts to isolate a type C from 20 plus Et_2NH, 2 moles of amine were added slowly to a solution of 20 which was then filtered and stripped. At low volume, explosive generation of HCl occurred, and an insoluble red gum remained. I interpret this to show the high acidicty of C, the red gum being a polymer of 32.[6] However, C (cis-trans mixture) was detected when < 2 moles of Et_2NH was slowly distilled into a cold solution of 20, and the solution itself was assayed. Nmr showed two singlets at $\delta \sim 5.2$ and ~ 5.3 plus unreacted 20; ir showed besides 20, absorptions at 1663, 1630, 1565, and 1538 cm^{-1}. These spectra are very similar to those of the known type C species,  $(Me_2N)(Cl)C{=}CH{-}COCH_3$.[111] When the solution was allowed to warm and stand, the type C nmr absorptions disappeared, the solution became red-purple, and the odor of HCl could be detected. No type G species was noted (absence of quartet(s) $\sim \delta$ 6.1; cf. Chapter I), nor was any 32 (D) in the solution, but there was a C-methyl absorption beside that of 20. This signal is attributed to an oligimer of the acetylene 32.

In the reaction of the ketone 20 with excess piperidine, the ultimate product is the type E product, $(C_5H_{10}N)_2C{=}CH{-}COCH_3$ (33), obtained this way much more conveniently and in far greater yield than by acetylation of $CH_2{=}C(NC_5H_{10})_2$.[114] Using approximately a stoichiometric amount (4 moles) of amine, the reaction with 20 could be easily followed by ir (Figure 1). The spectra show that at least one route to 33 is A → C → D → E. One sees the type C absorptions and the growth and decay of the C≡C band. The yield of 33 is too good for D to be an incidental product washed away during work-up. The only way D could not be an intermediate in the production of E would be if the reaction C → D were reversible. This is

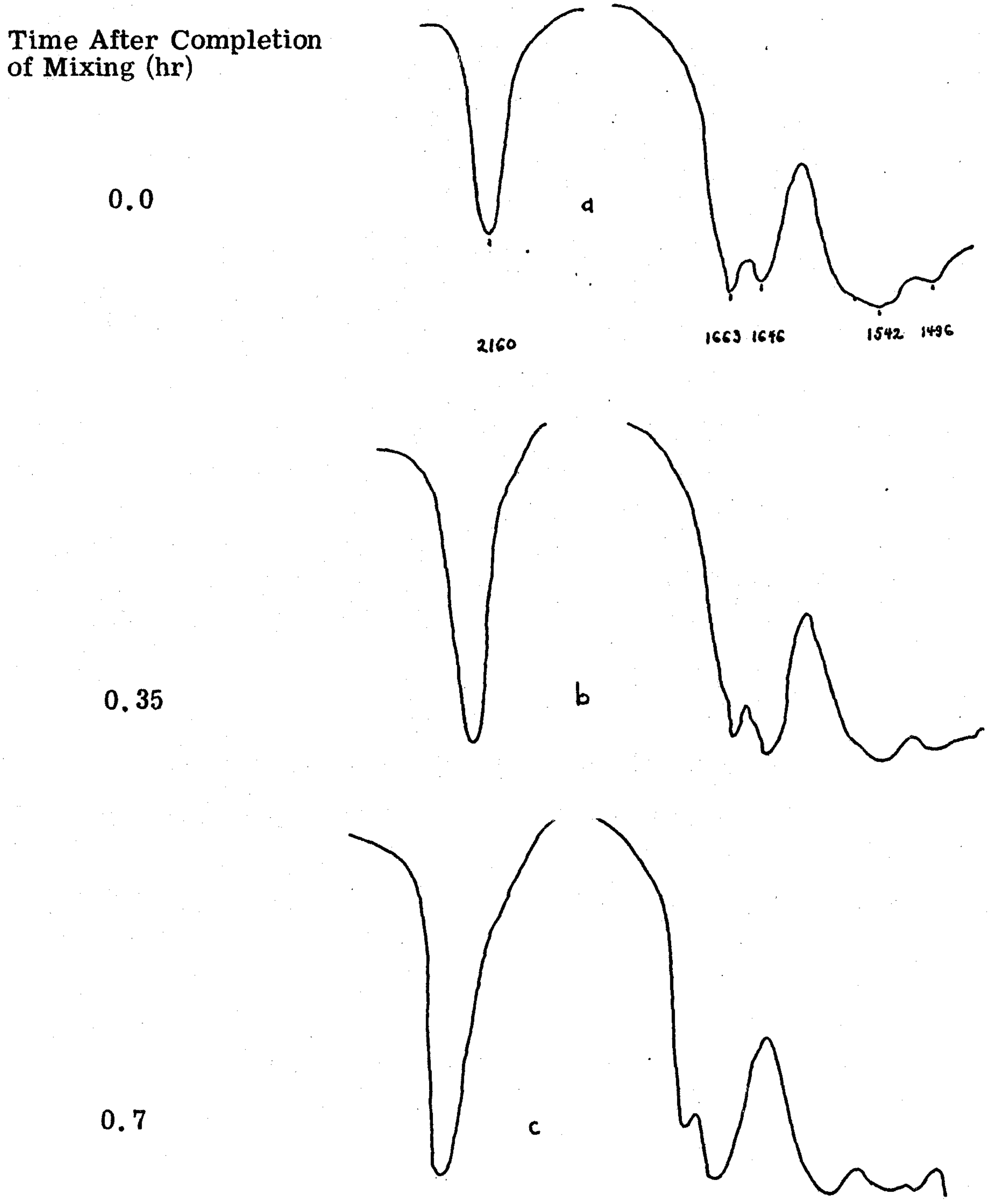


Figure 1. Infrared Spectra of the Reaction

Mixture of $Cl_2C{=}CH{-}COMe$ ($\underset{\sim}{20}$) + 4 pip H in Benzene

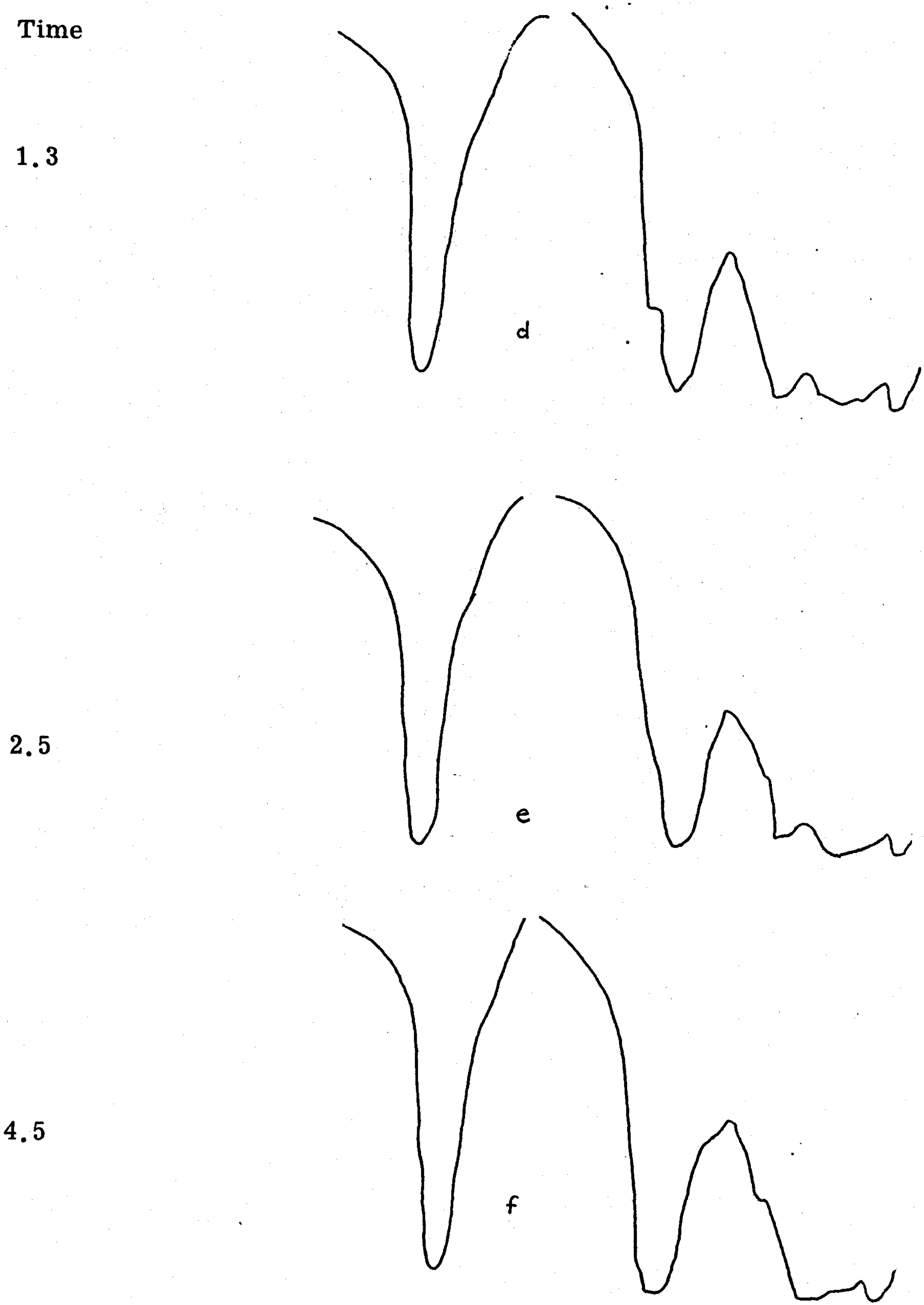


Figure 1 (Continued)

Time

17.5

Pure (pip)$_2$C=CH–COMe (33) in benzene (lower conc than a-g)

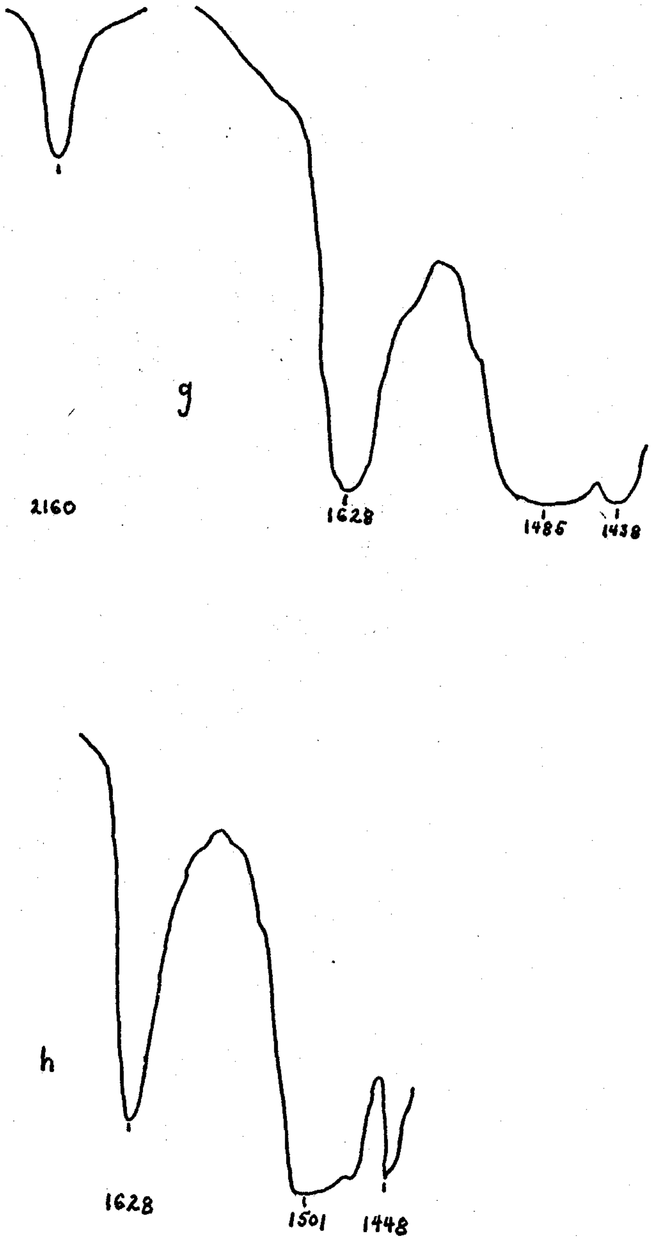
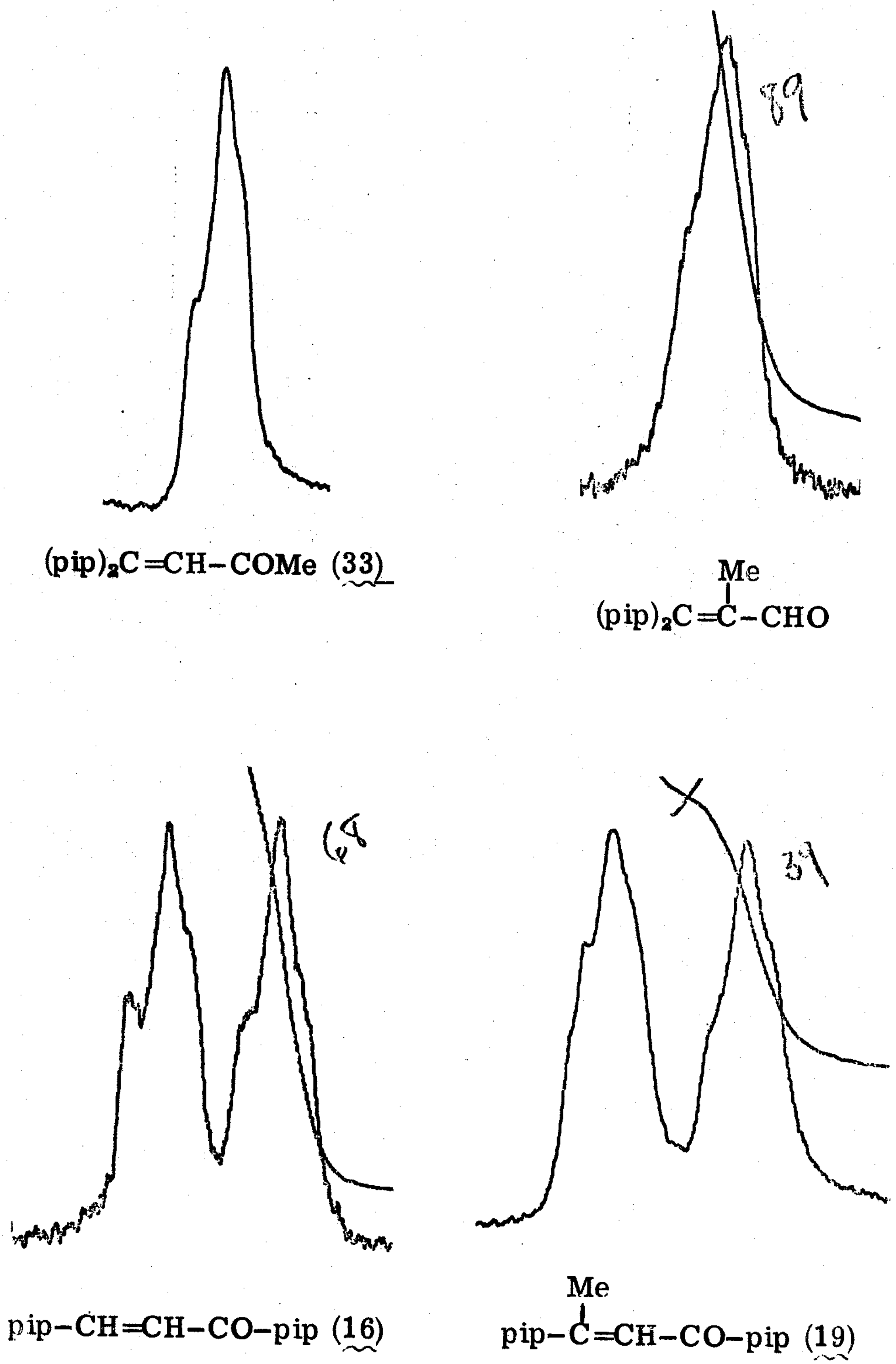


Figure 1 (Continued)

inconceivable in the presence of excess amine, which is a stronger base than D. The conversion D → C (and then → G) has been accomplished however with HCl in THF.[111] I do not contend that *all* 33 is produced *via* D in this reaction. That the reaction C → E is occurring simultaneously with C → D → E is inferred from the observation that the very strong type E band at $\sim 1505\ \text{cm}^{-1}$ is growing while the acetylenic absorption is still growing, and the rate of decay of the latter was quite slow even when a large excess of amine was used. The general question of whether C undergoes elimination to give D or substitution to give E is reminiscent of the behavior of simple alkyl halides with nucleophiles which are also good bases. That D can be a *precursor* of E is a complication which is usually not a problem with simple, as opposed to vinylogous, systems.

That 33 is not the isomeric vinylogous urea 19 is shown by comparison of its physical properties with authentic 33[114] and the different nmr spectrum from 19. It may be noted here that in the examples I have studied, vinylogous ureas with the same amine on both ends show magnetically nonequivalent α-amino protons, whereas those of the isomeric acyl ketenaminals are magnetically equivalent (Figure 2 and Paper II).

An explanation is in order regarding the ease with which C eliminates HCl. That C is *thermodynamically* acidic is not surprising; it is formally an HCl adduct of an ethynylogous amide, and amides are feeble bases. But this would apply *a fortiori* to the starting material 20 (A) since it is formally an adduct of an ethynylogous acid



$(\mathrm{pip})_2\mathrm{C{=}CH{-}COMe}$ (33)

$(\mathrm{pip})_2\mathrm{C{=}}\overset{\mathrm{Me}}{\mathrm{C}}\mathrm{{-}CHO}$

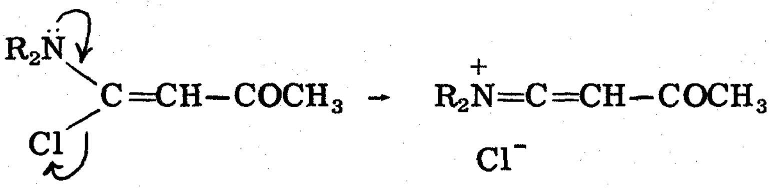
$\mathrm{pip{-}CH{=}CH{-}CO{-}pip}$ (16)

$\mathrm{pip{-}}\overset{\mathrm{Me}}{\mathrm{C}}\mathrm{{=}CH{-}CO{-}pip}$ (19)

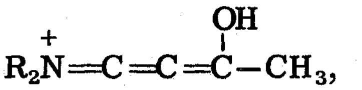
Figure 2. The α-Piperidino Nmr Resonances of Some Acyl Ketenaminals and Vinylogous Ureas.

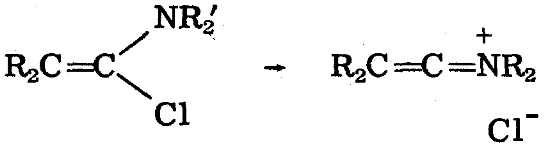
chloride, and acyl halides are even weaker bases than amides. Yet the conversion A → B is not observed.

Hence C must be kinetically highly acidic. I propose geminal anichimeric assistance as an explanation, i.e. internal displacement of the chlorine by the amino group:



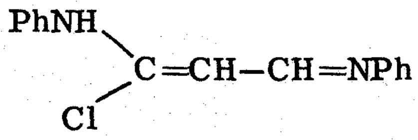
C C′

The loss of H^+ from the ketiminium salt C′ is then a typically facile β-elimination (α-H labilized by carbonyl) accelerated by the fact that the leaving group has already left and that C′ bears a positive charge. An allenic enol,  $\overset{+}{R_2N}=C=C=\overset{OH}{C}-CH_3$, may be an intermediate.[115] Ketiminium salts have been implicated in the substitution reactions of α-chloroenamines,[116]

 .

Experimental support of intermediacy of C′ is found in several observations. I have noted that the precipitate filtered from reactions of **20** with a deficiency of amine (< 3 moles) darkens as it dries; pure simple amine hydrochlorides do not do this. Also, in all the reactions of amines with **20**, the difficulty of stirring is maximum shortly after the addition is complete, implying formation of a solid which redissolves.

Finally, my nmr spectrum of the compound formulated as



$\mathrm{(PhNH)(Cl)C{=}CH{-}CH{=}NPh}$ (from reaction of the aldehyde **25** with aniline)[85a] shows a single unsplit absorption for all three aliphatic protons. Thus the compound is best described as a salt $\mathrm{[PhN{=}CH{-}\overset{+}{C}H{-}CH{=}NPh]Cl^-}$ (possibly in equilibrium with the covalent structure) with its various resonance structures, a tautomerization process exchanging the central and end hydrogens. The aldehyde **26** with aniline gives the amidine hydrochloride anil.[108]

The observation that in the conversion D → C ($\mathrm{Me_2N{-}C{\equiv}C{-}CHO}$ plus HCl in THF), a white precipitate forms which redissolves[6] suggests initial rapid salt formation followed by attack of chloride at the β-carbon, i.e. a ketiminium salt is an intermediate in the reverse of the C → D. reaction. Push-pull acetylenes (type E) with $\mathrm{HBF_4}$ give salts of their cyclic dimers, cyclobutadienes[115,117]; $\mathrm{BF_4^-}$ is a very poor nucleophile. Two other facts worth noting are that species like C but with α-*alkyl* are quite thermally stable,[118a] but the chlorine is very labile toward hydrolysis.[118b]

The ketone **20** with $\mathrm{Me_2NH}$ gave the type E product, $\mathrm{(Me_2N)_2C{=}CH{-}COCH_3}$ (**34**). This compound distilled without decomposition *in vacuo*. Its nmr spectrum showed a single N-methyl resonance even at -70° (cf. Paper II).

The AVDC's studied besides the aldehydes 25 and 26 and the ketone 20 all also gave type D products but not as easily or cleanly as 20. A mixture of the ketones 21a and b reacted with Et_2NH as did 20, giving a little type E product in THF. The phenyl ring absorptions confuse the ir spectrum somewhat, but I could easily observe the growth and decay of a strong band ~ 1540 cm^{-1} assigned to the type C intermediate and the growth of the very strong acetylenic absorption.

Unless the previously cited result concerning the reaction of 21a with tritiated dimethylamine[99] is incorrect, the formation of the type D species from 21a with Et_2NH implies that either the less hindered amine largely prefers the path C → E rather than C → D and/or that there is a very large isotope effect. The general statement that D is not formed from A plus R_2NH[39] is clearly incorrect.

The ester 29 reacted with Et_2NH to give ~ 4:1 mixture of D and E. This ratio varied only slightly with a variety of solvents and 29: amine ratios. Reaction of 29 with *i*-Pr_2NH was very slow at room temperature; prolonged refluxing in benzene or toluene gave some acetylenic product(s)), and the ir spectrum of the reaction mixture showed numerous carbonyl frequencies, suggesting some aminolysis of the ester linkage. Reaction of 29 with one mole of Et_2NH and excess Et_3N gave a dark solution and discolored precipitate; only a little intractable gum was obtained from the filtrate. Using *i*-Pr_2NH as the auxiliary base and one mole of Et_2NH still gave both D and E, ~ 4:1.

These results imply that in this particular system, most of the type product E comes from C rather via D. The constancy of the D:E ratio even when excess Et_2NH was present implies the conversion D → E must be very slow.

Several carboxamides made from the acid chloride 28 were allowed to react with *i*-Pr_2NH, preliminary experiments showing that reaction with Et_2NH did not give acetylenes. The root amide 30 and the N-*t*-butyl and N-phenyl amide reacted so slowly even in refluxing toluene that they were not further studied.

The N, N-diisopropyl amide (35) on prolonged refluxing with excess amine did form some type D compound, but disappearance of 35 simply stopped after several days. Attempts to isolate the acetylene gave a high melting white solid whose only multiple bond ir absorption was a very strong band at 1634 cm^{-1}! This curious result, for which I have no explanation, was not further investigated.

The nitrile 31 reacted with Et_2NH and *i*-Pr_2NH more readily than the ester 29. With Et_2NH, mostly the type E product was obtained; it has been implied that the conversion D → E in this system occurs rather readily.[109] Reaction of 31 with *i*-Pr_2NH in refluxing benzene effected total conversion of 31 to *i*-$Pr_2N{-}C{\equiv}C{-}CN$ (36) in 24 hours with no formation of type E product. This reaction is readily followed by ir; the product 36 shows two strong triple bond absorptions (Figure 3). Previously, the higher frequency absorption has been assigned to $\nu_{C\equiv C}$ in compounds like 36[109]; the reverse assignment was made for

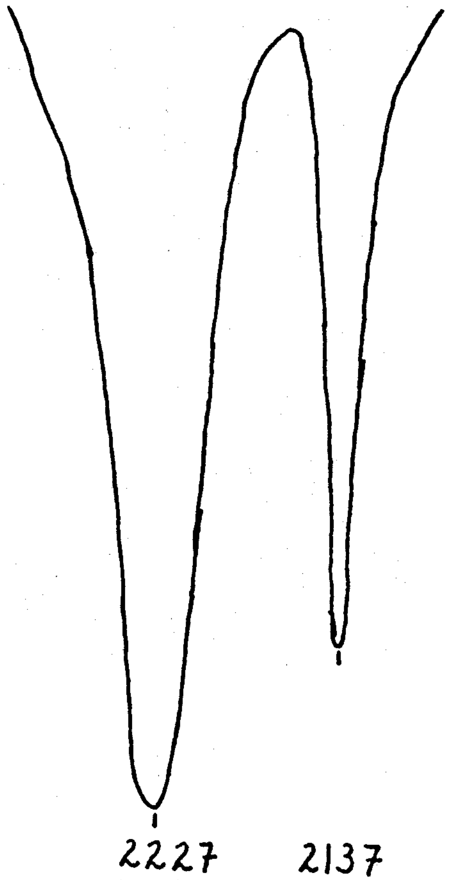


Figure 3. The Infrared Spectrum

$(Me_2CH)_2N-C\equiv C-C\equiv N$ (36)

the halocyanoacetylenes.[119] I believe it reasonable to recognize that the triple bond vibrations must be strongly coupled and assign the more intense higher frequency absorption to ν_{asym} and to lower to ν_{sym} for the whole conjugated system.

Experimental

Syntheses of Activated Vinylidene Chlorides.

General. Extensive experimental details are given only for new compounds or new methods; the reaction schemes for compounds prepared by reported methods were given in the previous discussion. Additions of one reagent to another were always done with efficient stirring unless otherwise stated. Spectral data were determined as in Chapter I. Data included in Papers I and II, attached, are not repeated here.

All AVDC's should be regarded as vicious vesicants. If spilled on the skin, immediate washing with soap and water (not organic solvents) is essential. The healing of blisters, which should not be lanced, is greatly speeded by frequent application of hydrocortisone ointment.

3,3-Dichloropropenal (25) was prepared in 42% yield by a standard method[85a]; bp 36-37° (20 mm) [lit. bp 64° (100 mm)[85a], 54° (56 mm)[79]]. Spectral data are in Paper I.

*3,3-Dichloro-2-methylpropenal (**26**)* was made by the reported procedure[86]; bp 44-46° (13 mm) [lit.[86] bp 47-49° (15 mm)]; ir (CCl_4) 1685 (s, C=O), 1589 cm^{-1} (s, C=C) [lit.[79] ir (neat) 1685, 1588 cm^{-1}]; nmr (neat) δ 1.69 (s, 3, methyl), 9.75 (s, 1, -C$\underline{H}$O).

*4,4-Dichloro-3-buten-2-one (**20**).* This compound was prepared by a modification of the reported procedures.[81,83] In a typical run, 205 g (1.54 mol) $AlCl_3$ was added to a solution of 125 ml (1.75 mol) AcCl, 175 ml (2.26 mol) $CH_2{=}CCl_2$ (**24**) and 300 ml CH_2Cl_2 at $T = < -8°$. The mixture was then stirred at -5° to -10° for one-half hour, in plain ice for 1-2 hours, and allowed to warm to ambient temperature over 2-3 hours. After decomposition with 1200 g cracked ice, the lower layer was separated, the aqueous phase extracted with CH_2Cl_2 (3 × 100 ml), and the combined organic phases extracted with saturated $NaHCO_3$ solution (3 × 100 ml) and once with 100 ml plain water. The muddy solution was partially dried with Na_2SO_4 and $MgSO_4$, partially stripped of CH_2Cl_2, and the residue steam distilled to yield 191 g (90%) impure **20** as a yellow liquid. This material was dried, refluxed several hours in a 30-cm Vigreux column under vacuum and then distilled, giving a mid-cut of 154 g (72%) **20** as a pale yellow liquid with a boiling range of $< 1°$; bp 55.3-56.2° (15.5 mm), 59.5-60.0° (18 mm) [lit.[81] bp 64° (22 mm)]. Impure **20** can be preserved with a little H_2O[81,84]; once thoroughly dry, it must be immediately purified as above to free it from dissolved HCl which causes an autocatalytic decomposition.[81] Spectral data are in Paper I.

3,3-Dichloro-1-phenylpropenone (21a) and 3,3,3-trichloro-1-phenylpropanone (21b). The procedure for the ketone 20 above, essentially the same as the reported one,[81,99] was used. From 77 ml (0.6 mol) PhCOCl, 75 ml (0.95 mol) 24, and 67 g (0.5 mol) AlCl$_3$ in 100 ml CH$_2$Cl$_2$ was obtained after distillation two fractions; the first (1), 12.1 g, had bp 166-168° (26 mm), the second (2), 62.6 g, had bp 169-178° (26 mm). Searles, *et al.*[81] report nmr and ir spectra for material with bp 140-150° (14 mm) consistent with pure 21a, but the original synthesizer[120] who reports an elemental analysis, did a lower pressure distillation [bp 82° (0.2 mm)[120]]. For my product, both fractions (1) and (2) contained 21b (nmr δ $\sim$4.1). Fraction (1) was $\sim$6:1 21a:21b; fraction (2) $\sim$1:2 21a:21b. Sorting out the spectra gives the following data: for 21a, ir (CCl$_4$) 1673 (s, C=O), 1565 cm^{-1} (s, C=C) [lit.[81,99] (neat) 1667, 1562 cm^{-1}]; nmr (CCl$_4$) δ 6.92 (s, 1, -C$\underline{H}$=CCl$_2$), 7.0-7.3 (m, 3, β- and γ-phenyl), 7.4-7.7 (m, 2, α-phenyl) [lit.[81] δ 7.16, 7.33-7.57, 7.75-7.95]. For 21b, ir (CCl$_4$) 1708 cm^{-1} (s, C=O), nmr δ 4.08 (s, -CO-C$\underline{H}_2$-CCl$_3$), aromatic H's in same envelopes as those of 21b. My total yield of both 21a and b amounts 68%.

The absorptions attributed above to 21b disappeared when a sample of the mixed ketones was stirred with aqueous NaHCO$_3$ for several yours. Since this showed that 21b yields 21a with even a weak base, the mixed ketones were used without separation in the reaction with Et$_2$NH described below.

4,4,1-Trichloro-3-buten-2-one (22a) and 4,4,4,1-tetrachloro-2-butanone (22b). Essentially the procedure for the ketone 20 was followed. After reaction of 43 ml (0.53 mol) $ClCH_2COCl$, 85 ml (1.1 mol) 24, and 66 g (0.49 mol) $AlCl_3$ in 100 ml CH_2Cl_2, the quenched mixture was directly steam distilled. The lower layer was separated, the aqueous phase (~ 500 ml) extracted with CH_2Cl_2 (2 × 50 ml), and the combined extracts dried as for 20. Stripping at 50°/31 mm left 78.5 g (81%) yellow liquid, which was mostly a 2:1 mixture of 22a and 22b. Repeated dry distillation (60-90°/16mm) converted most of the 22b to 22a; on chilling mixtures, the latter freezes out as white needles, mp ~ 38°, which are stable indefinitely at room temperature. The mixed ketones stored at room temperature darken slightly over several months. The mixture and solid 21a are terrible lachrymators, as would be expected from their structures; this fact discouraged separation efforts. Spectral data: For 21a, ir (CCl_4) 1727 (w-m) and 1702 (m-s) (both (?) C=O, cf. Paper I), 1572 cm^{-1} (C=C); nmr (CCl_4) δ 4.27 (s, 2, $ClC\underline{H}_2CO-$), 7.02 (s, 1, vinyl H). For 22b in neat mixture, nmr δ 4.10 and 4.29, equal intensity singlets; 21a had δ 4.19, 6.93 in the mixture.

1,1-Dichloro-4-methyl-1-penten-3-one (23) was prepared by the published procedure,[76] modified as for 20 but without steam distillation. From 21.4 ml (0.21 mol) i-PrCOCl, 30 ml (0.38 mol) 24, and 28 g (0.21 mol) $AlCl_3$ in 50 ml CH_2Cl_2 was obtained 34.3 g (65%) brown stripped crude which was almost entirely the saturated trichloroketone as with 21 a,b . Distillation gave 26.6 g lemon yellow liquid, bp 75-87° (22-24 mm), which was a 3:1 mixture of 23 and its saturated precursor. In the nmr spectrum of the neat mixture, the $(CH_3)_2CH-$ group resonances were nearly coincident, δ 0.92 (d, J = 7 Hz, methyl), 2.60 (septet, J = 7 Hz, methine). The saturated ketone had its $-C\underline{H}_2-$ resonance at δ 3.89; the olefinic one 23 had δ 6.75 for its vinyl H.

3,3-Dichloropropenoic acid (27). Method (1). From ketone 20. To 1050 ml (~ 0.73 mol) commercial chlorine bleach stated to be 5.25% NaOCl was added at 1°, 28 g (0.21 mole) 20 all at once with no stirring. The mixture was then stirred in cool water keeping $T < 25°$ by adjusting the stirring rate. After 2 hr, the colorless lower phase was nearly all $CHCl_3$ (nmr). The mixture was cooled to ~ 5°, and solid $NaHSO_3$ was added in small portions until the solution had $pH < 5$ (~ 23 g), keeping $T < 10°$. On slow addition of 125 ml 25% H_2SO_4, white needles appeared. The mixture was allowed to warm, the layers were separated, and the aqueous phase extracted with CH_2Cl_2 (8 × 100 ml). The combined organic solutions were dried over Na_2SO_4 and $MgSO_4$, and on stripping gave 14.3 g (50%) slightly yellowish needles, mp 70-73°. Recrystallization from CCl_4 (1 ml/g) gave 11.0 g (38%) 27, mp 75-76°, not as pure as material obtained by method (2) below.

Method (2). From ketones 22a, b. In an ice bath, 38.8 g (0.20 mol) of 2:1 mixture of 22a and b and 40 ml CH_2Cl_2 was stirred with 640 ml (0.45 mol) chlorine bleach, keeping $T < 6°$. After 1 hr, conversion was complete (nmr), and the lachrymatory effect of the of the solution nearly gone. The yellow lower layer was siphoned off, and $NaHSO_3$ was added as above (~ 14 g sufficed to acidify the solution). The pH was taken to <1 by addition of 40 ml 10 M H_2SO_4. Extraction with CH_2Cl_2 (5 × 60 ml) and further work-up as for method (1) gave 20.7 g (73%) near white needles, >98 mole% 27 by nmr and suitable for conversion to the acid chloride 28 and ester 29. Two recrystallizations from CCl_4 gave white needles, mp 76-77° [lit.[88] mp 76-77°]. Spectral data are in Paper I. Anal. Calcd. for $C_3H_2Cl_2O_2$: C, 25.56; H, 1.43; Cl, 50.31. Found: C, 25.45; H, 1.40; Cl, 50.40.

The acid 27 is stable in acid even hot, but with warm base yields $HC{\equiv}C{-}Cl$, which is explosive with air.[121] This was dramatically confirmed when a small amount was refluxed with aqueous $NaHCO_3$. A fruity HCN-like odor was apparent at the condenser top, and on removing the heating mantle, a spit of flame shot the length of the condenser, blacking the inside.

3,3-Dichloropropenoyl chloride (28). Twenty-seven ml (0.37 mol) $SOCl_2$ and 27.5 g (0.195 mol) acid 27 were refluxed until the pot temperature ceased to rise (~ 1.5 hr). Distillation in a semi-micro apparatus, overdriving the condenser slightly, gave 23.7 g (76%) 28 as a colorless liquid, bp 51.6-52.2° (18 mm) [lit. bp 147° (atm),[87] 53° (20 mm)[90]]. This material was free of $SOCl_2$ (absence of 1234 cm^{-1} absorption in ir spectrum). Spectral data for 28 are in Paper I.

Hydrolysis of the trap material and pot residue (anhydride ?) from the distillation gave 2.6 g acid 27; thus the yield of 28 from converted 27 was 93%.

3,3-Dichloropropenamide (30). To 20 ml (~ 0.3 mol) cold concentrated aqueous NH_3, 8.0 g (0.05 mol) 28 was added in small squirts over 10 min. After stirring for 10 min., the slurry was filtered to afford after air drying of the off-white solid, 6.7 g (95%) 30, mp 112-114° [lit.[87] mp 112-113°].

N-*t*-Butyl 3,3-dichloropropenamide and N-phenyl 3,3-dichloropropenamide. To a cooled solution of 1.6 g (0.01 mol) 28 in CCl_4 was added dropwise 1.48 g (sl $>$ 0.02 mole) *t*-$BuNH_2$ in 10 ml CCl_4. The mixture was allowed to warm and filtered. Evaporation of the filtrate and recrystallization of the residue from CCl_4 gave 1.50 g (76%) t-Bu amide as a white solid; mp 101-102°; ir (CCl_4) 1655, 1597, 1535, 1518 cm^{-1}; nmr (CCl_4) δ 1.37 (s, 9, methyls), 6.38 (s, 1, vinyl H), 6.80 (broad singlet, 1, -N*H*-).

The anilide of 27 was similarly obtained using the same amount of 28 and CCl_4, and 1.87 g (0.02 mol) aniline; 1.66 g (77%) white needles, mp 119-121° [lit.[90] mp 120-122°].

Methyl 3,3-dichloropropenoate (29). A mixture of 28.2 g (0.20 mol) acid 27, 100 ml (large excess) dry methanol, and 11 ml conc. H_2SO_4 was refluxed 60 hr. The yellow mixture was then poured into 150 ml water, the layers separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 30 ml). The organic extracts were washed with 35 ml water and twice with 30 ml nearly saturated $CaCl_2$ solution. After drying with $MgSO_4$, distillation gave a mid-cut of 24.7 g (79%) 29 as a colorless liquid, bp 57.7-58.8 (18 mm). This compound readily freezes to large transparent spars of mp ~ 15°. Spectral data and analysis are in Paper I.

Unless scrupulously free of methanol, the compound **29** slowly yellows. For extended storage, the low melting 10-20% was decanted away, and the material stored frozen. Inhalation of the very pleasant smelling vapor causes severe but transient headaches and mucosal edema.

3,3-Dichloropropenonitrile (**31**). Chloral cyanohydrin was prepared via the bisulfite compound. It is essential to work fast and keep solutions cold since the latter is unstable.[122] The cyanohydrin is discolored if the temperature is allowed to rise above ~ 20° during the addition of the NaCN solution. A better yield of cyanohydrin is obtained by use of gaseous HCN,[123] but my method is safer.

To a solution of 450 ml (~ 2.6 mol) cold saturated aqueous $NaHSO_3$ (~ 44 wt %, sp. gr. > 1.36) was added in small squirts 222 g (1.5 mol) chloral, keeping $T < 10°$. (Alternatively, a saturated aqueous solution of chloral hydrate can be used.) The resulting very thick white slurry was diluted with 50 ml water, and a solution of 98 g (2.0 mol) NaCN in 175 ml water was added in small portions, keeping $T < 15°$, over ~ 0.5 hr (HOOD). Most of the white solid dissolved, and two liquid layers appeared during this addition. The mixture was allowed to stand while warming to ambient temperature with occasional shaking for about 1 hr, ~ 200 ml water was added to dissolve gelatinous white material, and the lower layer was drawn off.

The aqueous phase was extracted with CH_2Cl_2 (3 × 100 ml), the combined organic solutions were washed with water (2 × 60 ml) and saturated NaCl solution (2 × 50 ml), and dried with Na_2SO_4 and $MgSO_4$. Stripping the solution (39°/28 mm) afforded 177 g (67%) of the cyanohydrin as somewhat yellowish fine needles, suitable for acetylation. Recrystallization of a small sample from CCl_4 gave white needles, mp 58-59° [lit. mp 58-59°,[124] 61°[123]]; nmr (CCl_4) δ 4.76 (broad singlet, 1, -O$\underline{H}$), 5.02 (s, 1, -C$\underline{H}$(OH)CN).

The cyanohydrin was acetylated by the reported method,[105] except that the product was vacuum distilled (bp 103-110°/17 mm) after distilling off AcOH and excess Ac_2O. From 157 g (0.90 mol) cyanohydrin and 105 ml (1.12 mol) Ac_2O was obtained 142 g (73%) of the acetate with mp $> 28°$ [lit.[105] mp 31°] as large white crystals with a biting odor. Ir(CCl_4) 2248 (vvw, C≡N), 1780 cm^{-1} (s, C=O); very feeble C≡N absorptions are typical of cyanohydrins and their esters.[125] Nmr (CCl_4) δ 2.26 (s, 3, methyl), 6.00 (s, 1, -C$\underline{H}$-(OAc)CN).

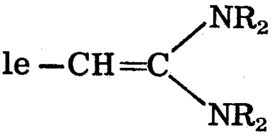
The cyanohydrin acetate was converted to the nitrile **31** by reduction with Zn in hot THF.[104] From 86.6 g (0.40 mol) of the acetate and 26.8 g (0.41 mol) Zn dust in 350 ml THF was obtained 35.4 g (71%) nitrile **31**, colorless liquid, bp 138-141° (739 mm) [lit.[79] bp 140-141° (745 mm)]; ir (CCl_4) 2232 (w-m, shp, C≡N), 1595 (m, sh), 1583 cm^{-1} (m-s, C=C) [lit.[79] ir (neat) 2232, 1582 cm^{-1}]. This compound has a strong broad absorption at ~ 795 cm^{-1}, of which the 1595 cm^{-1} shoulder is probably a Fermi-resonance enhanced overtone. Nmr (neat) δ 5.98 (s, vinyl H).

The nitrile 31 freezes to colorless spars, mp ~ 10°, and can be purified by decantation.

Hydrolysis of 31 to the acid 27 was accomplished as follows: To 8.5 ml cool 90% H_2SO_4, 2.44 g (0.02 mol) 31 was added, and the solution allowed to stand 48 hr. After pouring over 25 g cracked ice, the slurry of the crude pinkish amide (mp 107-111°, mmp with authentic 30 108-112°), was refluxed 2 hr. On cooling, 2.40 g (85%) slightly stained long needles of 27 crystallized, mp and mmp with authentic 27 75-76°, after washing with a little ice water and air drying. It is somewhat surprising that 27 crystallizes anhydrous from water, but this is the case.

Reaction of Activated Vinylidene Chlorides with Secondary Amines

General. The general comments of Chapter I and the above section on syntheses of AVDC's apply. For most products, no claim is made for analytical purity. In particular, the "push-pull" acetylenes are generally high-boiling thermally unstable liquids.[6]

The very intense lower frequency ir absorption(s) in the double-bond stretching region, assigned to "C=C" in the acyl ketenaminals undoubtedly involves the whole  $-CH{=}C\begin{smallmatrix}NR_2\\NR_2\end{smallmatrix}$ system.[115] As mentioned in Chapter I, all the (formally) double-bond stretching vibrations are strongly coupled in polarized ethylenes.

Reactions of the aldehydes 25 and 26 with piperidine are described in Paper II.

The reaction of the aldehyde 25 with Et_2NH gave unclear results. In several experiments, to 1.25 g (10 mmol) 25 in 10-15 ml THF was added 3.5-4.0 ml (35-40 mmol) amine in a like amount of solvent at -15° to +5°. White precipitate appeared. Ir spectra of the supernate immediately after addition of the amine and after several hours showed occasionally a weak absorption at $\sim 2150\ cm^{-1}$ and always absorptions at 1642 (s), 1610 (m-s), and 1565 cm^{-1} (vs). Attempted work-up gave insoluble and otherwise intractable gums which were not further studied.

Under similar conditions but using CCl_4 as solvent, the nmr spectrum of the supernate presented a confusing picture, showing numerous resonances between δ 4.3 and 10.1.

Reaction of the aldehyde 25 with aniline in acetic acid, done exactly as described,[85a] gave the product originally formulated as 1-phenylimino-3-anilino-3-chloro-2-propene, Ph NH–C(Cl)=CH–CH=NPh, as a yellow solid, mp 142-145° [lit.[85a] mp 144-146°]. The nmr spectra showed all the aliphatic hydrogens to be equivalent; nmr (F_3CCOOD) $\delta \sim 7.1$ (broad multiplet, 10, aromatic H's), 8.74 (broad singlet, 3, aliphatic H's; nmr (DMSO-d_6) 3.21 (s, 3, aliphatic H's), ~ 7.2 (multiplet, 10, aromatic H's).

4-Diethylamino-3-butyn-2-one (32). In a typical preparation, 103 ml (1.00 mol) Et_2NH was added dropwise to 27.8 g (0.20 mol) ketone 20 in 800 ml ether keeping $T < 10°$ (20 min). White precipitate began appearing immediately. After stirring 1 hr in ice, the solution was allowed to warm to ambient temperature (22-24°) over 1-2 hr, and stirred 3-5 hours (stirring becomes easier.) Filtration gave

21.2 g (97%) amine hydrochloride. Stripping of the yellow filtrate gave 27.2 g (97%) crude 32 as a brownish liquid whose nmr spectrum showed 1-2% olefin (δ ~ 4.2). Distillation from a little K_2CO_2 proceeded with 70% recovery, giving a middle cut of 19.0 g (68%) 32 as a yellowish liquid, bp 62-67° (0.15-0.18 mm); ir (CCl_4) 2162 (vs, C≡C), 1636 cm^{-1} (s, C=O); ir (DCE) 2155, 1627 cm^{-1}; ir (MeCN) 2155, 1630 cm^{-1}; nmr (neat) δ 0.9 (t, 6, J = 7 Hz, $C\underline{H}_3CH_2N$-), 1.79 (s, 3, $C\underline{H}_3CO$-), 2.78 (q, 4, J = 7 Hz, $CH_3C\underline{H}_2N$-).

This material turns brown on storage at -15° under N_2; the ir spectrum showing slow growth of new absorptions in the 1500-1750 cm^{-1} region.

Using CCl_4 or benzene in the preparative reaction gives material containing 4-6% olefin. Inverse order of addition in ether gave the same results as above.

Hydrogenation of small sample of 32 (25°, 1 atm, 5% Pd-on-C, cyclohexane), withdrawing aliquots for nmr assay at intervals, showed new resonances growing in at δ 1.74 ($C\underline{H}_3$–CO in 32 at δ 1.62 in this solvent), 4.78 (d, J = 13 Hz), and 7.17 (d, J = 13 Hz), enhanced on addition of authentic Et_2N–CH=CH–$COCH_3$ (Chapter I).

For the reaction to observe the type C intermediates (Et_2N–C(Cl)=CH–Ac) of 32, 14.0 g (sl $<$ 0.2 mol) Et_2NH was allowed to diffuse from a flask held at 30-35° into a 0° solution of 13.9 g (0.1 mol) 20 in 75 ml CCl_4/10 ml dioxane over 27 hours. The nmr spectrum of an aliquot of supernate showed four kinds of acetomethyls, the ketone 20 vinyl H at δ 6.62, and two singlets at δ 5.18 and 5.32, assigned to *cis* and *trans* type C.[111] On standing at ambient temperature for 24 hr, the mixture turned red-brown, and the nmr spectrum became simpler, showing only two acetomethyls and the vinyl H of **20** as the only olefin signal.

In a similar run, using only one mole of Et_2NH per mole of **20** and just CCl_4, the ir spectrum of an aliquot showed absorptions at 1704 (w-m, C=O in **20**), 1663 (m-s), 1630 (m-s), 1565 (s), and 1538 cm^{-1} (vs). The latter four bands are assigned to *cis* and *trans* type C.[111]

*4,4 bis(Piperidino)-3-buten-2-one (**33**).* The best *preparative* procedure and the physical data are described in Paper II.

For the mechanism study (Figure 1), 60 ml (0.6 mol) amine were added rapidly to 20.8 g (0.15 mol) **30** in 200 ml benzene, keeping $T < 15°$; stirring was most difficult toward the end of, and immediately after completion of the addition. Ir spectra of aliquots were taken at the times indicated in Figure 1.

*4,4-bis(Dimethylamino)-3-buten-2-one (**34**).* This compound was made similarly to **33**, using 85 ml (~ 1.25 mol) Me_2NH, in 700 ml ether with addition of 34.75 g (0.25 mol) **20** and stirring in ice for 48 hr. Distillation gave 26.6 g (68%) **34** as a light orange liquid, bp 64-72° (0.2 mm) [lit.[99] bp 61-63° (0.05 mm)]. Ir (CCl_4) 1623 (s, C=O), 1511 (vs, C=C), 1471 cm^{-1}; ir (CH_2Cl_2) 1606 (s, C=O), 1520 (vs, C=C), 1471 cm^{-1}; nmr δ 1.92 (s, 3, $C\underline{H}_3CO$-), 2.76 (s, 12, N-methyls), 4.34 (s, 1, vinyl H); see also footnote 3 in Paper II.

Reactions of the mixed ketones 21a, b with diethylamine. To a solution of 4.6 g (~ 20 mmol) ~ 1:2 21a:21b in 85 ml THF was added dropwise 13 ml (120 mmol) Et_2NH, T = 0-10°. A copious white precipitate appeared; the supernate was light green. The mixture was then allowed to stir at ambient temperature. Ir spectra of aliquots showed the disappearance of the starting material absorptions, the growth and decay of a strong split band at 1538 cm^{-1} (attributed to type C intermediate), and the growth of a very strong absorption at 2160 cm^{-1} accompanied by a strong one at 1623 cm^{-1}. No strong band near 1510 cm^{-1} noted in 33 and 34 appeared. Stripping the filtered solution gave 4.67 g (~ 105%) crude $PhCO{-}C{\equiv}C{-}NEt_2$ as an orange oil which resisted attempts to crystallize it. Since this reaction was done only to show the generality of the production of type D acetylenes from AVDC's and in hopes of easily obtaining a *solid* type D product, the product was not further studied.

Reaction of the ester 29 with diethylamine. A number of runs were made, whose results are summarized in the description below.

To a solution of 3.10 g (20 mmol) 29 in 15-25 ml ether, THF, benzene, or CCl_4 was added 6.0-7.0 ml (60-70 mmol) Et_2NH at -20 to +25°. White precipitate and slight heating occurred. Following the reaction by ir showed the decay of the absorptions of 29 and growth of those of methyl 3-diethylaminopropynoate (type D) at 2190 ($C{\equiv}C$) and 1690-1695 cm^{-1} ($C{=}C$) [lit.[6] for Me_2N– homolog 2195, 1696 cm^{-1}], with slower growth of bands at ~ 1650 and ~ 1580 cm^{-1} (assigned to $C{=}O$ and $C{=}C$ in $(Et_2N)_2C{=}CH{-}COOCH_3$ (type E)).

After filtration and stripping of the solution, the nmr spectrum showed that the residual orange oil was ~ 4:1 mixture of D:E; nmr (neat) δ_D 1.01 (t, J = 7 Hz, $C\underline{H}_3CH_2N$-), 2.92 (q, J = 7 Hz, $CH_3C\underline{H}_2N$-), 3.42 (s, $-OC\underline{H}_3$) [lit.[78] 1.20, 2.97, $\underline{\underline{4}}$.35 (sic!)]; δ_E 0.99 (t, J = Hz, $C\underline{H}_3CH_2N$-), 2.92 (q, J = 7 Hz, $CH_3C\underline{H}_2N$-), 3.35 (s, $-OC\underline{H}_3$), 4.67 (s, vinyl H).

Reaction of 29 with i-Pr_2NH was very slow at 20-25°. When one equivalent of Et_2NH or Pr_2NH was added to a solution of 29 containing excess i-Pr_2NH, the results were similar to those above. Refluxing 29 with i-Pr_2NH in benzene or toluene for up to six weeks gave some acetylene but a melange of other products.

Reaction of the amide 35 with diisopropylamine. Reaction of the acid chloride 28 with the amine stopped at the amide 35 at ambient temperature. To a solution of 1.60 g (10 mmol) 28 in 25 ml CCl_4 was added at 0-10° 6.50 g (64 mmol) amine, and the solution stirred at 23° for several hours. Filtration gave 1.37 g (10 mmol) amine hydrochloride. The ir spectrum of the filtrate showed absorptions at 1642 (s, C=O) and 1604 (m, C=C); the nmr showed a singlet at δ 6.65 for the vinyl H.

In 50 ml benzene, 3.2 g (20 mmol) 28 and 21 ml (150 mmol) amine were refluxed for 7 days after initial slow amine addition. White precipitate gradually increased in quantity. The ir spectra of aliquots showed growth of absorptions at 2168 (vs, C≡C) and 1608 cm^{-1} (s, C=O) [lit.[6] for $Me_2N-C\equiv CONMe_2$ 2190, 1619 cm^{-1}] and no other absorptions between 1500 and 2400 cm^{-1}, except 1642 cm^{-1}

(amide 35). The spectra stopped changing after 7 days although excess amine was present. Stripping of the filtrate gave a yellowish solid, which after recrystallization from CCl_4, gave 1.2 g white crystals mp 142-144°; ir (CCl_4) 1634 (s), 1473 (w-m), 1438 (m) and no other multiple bond absorptions.

3-Diisopropylaminopropynonitrile (36). Preliminary studies of the reaction of the nitrile 31 with amines showed that it reacted faster than the ester 29, giving with Et_2NH a product with strong absorptions at 2196 and 1583 cm^{-1} (latter vs), presumably the type E species.

To prepare 36, a mixture of 2.44 g (20 mmol) 31, 20 ml (~ 150 mmol) i-Pr_2NH and 80 ml benzene was refluxed for 24 hours. Following the reaction by ir showed the decay of the 1583 cm^{-1} band in 31 and the growth of two triple bond absorptions (Fig. 3). Filtration and stripping gave 5.12 g (92%) amine hydrochloride and 2.67 g (89%) 36 as an orangish oil. Ir (benzene) 2227 (vs, ν_{asym}), 2137 cm^{-1} (s, ν_{sym}); nmr (neat) 1.10 (d, 6, J = 6.5 Hz, methyls), 3.12 (septet, 1, J = 6.5 Hz, methine H).

For a variety of compounds $R_2N-C{\equiv}C-CN$ made from the amine and $Cl-C{\equiv}C-CN$, strong bands at 2270 and 2180 cm^{-1} are reported[109] as a general property under unspecified conditions. I have no explanation for the dissimilarity of these values with mine; it is noteworthy that the frequency differences are the same in the reported values and in mine.

CHAPTER III

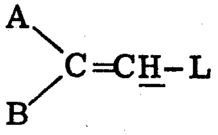
Spectral Correlations

Introduction

In this brief chapter, some general observations in regard to the spectra (especially nmr) of the compounds described in Chapters I and II are made. Spectral arguments made previously with respect to product identification and those of Papers I and II are not repeated below.

Since nmr spectra were usually measured for the purpose of product identification or purity determination, the conditions under which the spectra were taken were not uniform. Accordingly, the discussions below are discursive rather than formal and rigorous. For assertions below, references are usually cited only for inferences from data not in Chapters I and II or the attached Papers I and II.

The α-Vinyl Proton Chemical Shift in the Ethylenes

The prominent feature of the α-vinyl chemical shift in the various olefins,  $(A)(B)C{=}C\underline{H}{-}L$ (A and B = various combinations of Cl, H, CH_3, R_2N; L = carbonyl function or CN), is the failure of the α-vinyl δ to show a regular dependence on the electronegativity of L, contrasted with the very clear and expected dependence on the nature of A and B, especially on going from -Cl to $-NR_2$.

Thus, the AVDC's, $Cl_2C{=}CH{-}CO{-}X$, all have chemical shifts between δ 6.0 and 7.0, a considerable range; but the values do not increase regularly with increasing electronegativity of X, as would be expected from a simple inductive effect.[51] In the corresponding *mono* chlorovinyl carbonyl compounds (A = Cl, B = H or CH_3), this same phenomenon exists. For both $Cl_2C{=}CH{-}L$ and $ClCH{=}CH{-}L$, the nitriles, L = CN, have the chemical shift at slightly higher field than the corresponding compounds with L = carbonyl function.[45]

It was reliance on the typical range of δ 6-7 for $Cl_2C{=}C\underline{H}{-}COX$ which led to the conclusion that in the preparations of the ketones **21a**, **22a**, and **23**, the desired products were accompanied by their saturated HCl adducts with the group $CO{-}C\underline{H}_2{-}CCl_3$, δ ~ 4.0. Similarly, the *absence* of a signal near δ 4 in the compounds considered in Paper I gave me confidence that the duplicity of ir carbonyl absorptions was *not* due to the presence of both $Cl_2C{=}CH{-}COX$ and the $Cl_3C{-}CH_2{-}COX$.

When A and/or B changes from Cl to R_2N, there is a large upfield shift of the subject resonance to ~ δ 5 or higher. This is expected on an intuitive basis from resonance forms of type $R_2\overset{+}{N}{=}\overset{|}{C}{-}\overset{-}{C}H{-}L$, and calculations showing a partial negative charge at the α-carbon have made.[1b] In the systems I have studied, a narrower distinction can be made. Thus, for A = R_2N, B = Cl, δ = 5.1-5.3; for A = R_2N, B = H or CH_3, δ = 4.9-5.1; for A = B = R_2N, δ = 4.2-4.7. These ranges are broad, but large differences have been confirmed for pairs of isomers. In a mixture of $(pip)_2C{=}C\underline{H}{-}CHO$ and pip-CH=C$\underline{H}$–CO–pip, the chemical shift of the former is δ 4.18, of the latter δ 4.91. Similarly in a mixed nmr spectrum of the acetyl ketenaminal 33 and the isomeric vinylogous urea 19, the values are δ 4.25 and 4.80, respectively.

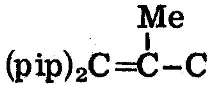
The effect of increased negative charge at the α-vinyl carbon on going from A, B = Cl to A, B = R_2N is also shown when there is an α-methyl. Thus, the chemical shift of the methyl in the aldehyde 26 (δ 1.68) moves to δ 1.47 in $(pip)_2C{=}C(CH_3)CHO$; the latter value is at quite high field for a vinyl methyl.[16, 51]

Infrared Correlations

The "push-pull" acetylenes, $R_2N{-}C{\equiv}C{-}L$. For these compounds (other than the nitrile 36 whose spectrum is discussed in Chapter II), the noteworthy feature is the nearness of the carbonyl stretching frequency to those of the compounds of which they are ethynylogs, i.e. the nearness of $\nu_{C=O}$ in these compounds to that of $\nu_{C=O}$ in $R_2N{-}COX$. Because of the large frequency difference between $\nu_{C\equiv C}$ and $\nu_{C=O}$ in these compounds, coupling of the vibrations must be much less[126] than in the related ethylenes.[127]

Thus, $\nu_{C=O}$ is at 1636 cm^{-1} for the ethynylogous acetamide 32 and is reported at 1644 cm^{-1} for the homologous dimethylamino compound.[6] These values are not very different from those of simple tertiary amides.[128] Similarly, the ethynylogous urethane, $Et_2N{-}C{\equiv}C{-}COOMe$ has $\nu_{C=O} \sim 1692$ cm^{-1}, very near that of tertiary urethanes.[129]

Since the effect of an α,β acetylenic linkage on $\nu_{C=O}$ is only about that of an olefinic one,[130] the ethynyl group in the "push-pull" alkynes must be acting as a conduit for electron density from the amino group. The frequency of $\nu_{C=O}$ in 32 is near that of $\nu_{C=O}$ in a number of β-enaminoketones, but "$\nu_{C=O}$" in the latter is a coupled vibration often consisting of two absorptions due to rotational isomerism.[23a]

The vinylogous urea 16 and the acyl ketenaminals. In connection with the studies described in Paper II, I was surprised to note that 16 had a higher frequency $\nu_{C=O}$ than either of its isomeric acyl ketenaminals,  $(\mathrm{pip})_2\mathrm{C}{=}\overset{\mathrm{Me}}{\mathrm{C}}{-}\mathrm{CHO}$ or 33. However, simple di-tertiary ureas have $\nu_{C=O}$ near 1660 cm^{-1},[131] a value somewhat higher than that typical of tertiary carboxamides; this is contrary to what one would expect on simple electronic grounds alone. The picture in the vinylogous systems is complicated by the fact that the fairly closely spaced double-bond absorptions in these compounds are undoubtedly coupled[23a] and therefore assignment of "$\nu_{C=O}$" to one and "$\nu_{C=C}$" to the other cannot be taken too literally.

It may simply be noted that in the vinylogous urea 16, the two absorptions are of comparable intensity, whereas in the ketenaminals, the lower frequency band is more intense, especially in 33 (see Fig. 1, Chapter II). This fact was also noted in the spectrum of $(Et_2N)_2C{=}CH{-}COOMe$, the minor product of the reaction of the ester 29 with Et_2NH.

The AVDC's, $Cl_2C{=}CH{-}COX$. These compounds showed the usual influence of the nature of X on the (primarily) carbonyl stretching frequency plus splitting attributed to rotational isomerism (Paper I). An additional comment is appropriate in regard to the spectrum of the amide 35 (X = N(i-Pr)$_2$). For this compound, there were just two absorptions in the double-bond stretching region (1642, 1604 cm^{-1}) with the 1642 cm^{-1} absorption much more intense. This suggests strong coupling of the double-bond vibrations, as for the triple bond ones of the nitrile 36. By analogy, a reasonable assignment is ν_{asym} for the more intense band and ν_{sym} for the less intense one rather than $\nu_{C=O}$ and $\nu_{C=C}$ for either band separately.

PAPER I

The following manuscript has been published with minor editorial changes: James B. Ellern and Harry B. Gray, *J. Org. Chem.*, **37**, 4485 (1972).

Rotational Isomerism in β,β-Dichlorovinyl Carbonyl Compounds

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Abstract: Four of the title compounds show two carbonyl stretching frequencies in their ir spectra. This is attributed to rotational isomerism about the olefin-carbonyl single bond.

In connection with a synthetic effort, we have prepared several of the title compounds, $Cl_2C{=}CH{-}CO{-}X$, X = H(1), Cl(2), CH_3(3), and OCH_3(4)[2]. These compounds show two bands in the carbonyl stretching frequency region of their ir spectra. The studies of Dabrowski and co-workers on the related mono β-chlorovinyl compounds[3a,b,c] suggest that this phenomenon is due to s-cis, s-trans[4] isomerism about the olefin-carbonyl bond.

Infra-red absorption bands in the 1500-1800 cm^{-1} region and nmr chemical shifts are set out in Table I. Inspection of the ir data

TABLE I

SPECTRAL DATA FOR THE COMPOUNDS Cl_2 C=CH-CO-X

		IR Absorption Bands (cm^{-1})		
X	Solvent	C=O^a	C=C^a	NMR(δ)
H	CCl_4	1733(w, shp)(A) 1688(vs) (B)	1591(s, sh) 1585(s) 1569(m)	6.25(d, 1, J=6.7 Hz $Cl_2C{=}C\underline{H}$) 9.56(d, 1, J=6.7 Hz -C$\underline{H}$O) (neat liquid)
	CH_3CN	1727(w, brd)(A) 1687(vs) (B)	1595(s, sh) 1585(s) 1570(m, sh)	
Cl	CCl_4	1789(s) (A) 1766(s-vs) (B)	1575(s, sh) 1570(vs) 1557(m, sh)	6.72(s) (neat liquid)
	CH_3CN	1790(m-s) (A) 1765(vs) (B)	1576(vs, sh) 1571(vs) 1558(m-s, sh)	
CH_3	CCl_4	1708(s) (A) 1678(m-s) (B)	1585(s) 1577(s, sh) 1574(vs) 1557(m, sh)	2.03(s, 3, $C\underline{H}_3$) 6.42(s, 1, $Cl_2C{=}C\underline{H}$) (neat liquid)
	C_2Cl_4	1707(s) (A) 1676(m-s) (B)	1583(s) 1576(s, sh) 1571(vs) 1557(m, sh)	
	$CHCl_3$	1701(s) (A) 1671(m-s) (B)	1584(s) 1576(s, sh) 1572(vs) 1560(m)	
	CH_2Cl_2	1702(s) (A) 1673(m-s) (B)	1584(s, sh) 1576(vs, sh) 1572(vs) 1557(m)	
	CH_3CN	1703(s) (A) 1673(m) (B)	1587(s, sh) 1574(vs) 1569(vs, sh) 1557(m)	

TABLE I (cont'd)

X	Solvent	C=O[a]	C=C[a]	NMR(δ)
OCH_3	CCl_4	1742(vs)	(A) 1617(m, sh)	3.59(s, 3, $OC\underline{H}_3$)
		1718(s)[b]	(B) 1608(vs)	6.29(s, 1, $Cl_2\overline{C}=C\underline{H}$)
				(neat liquid)
	CH_3CN	1733(vs)	(A) 1618(s, sh)	
		1718(s-vs, sh)[b]	(B) 1609(vs)	

[a] These designations refer to the generally accepted spectral regions and do not necessarily imply assignment; see the discussion below.

[b] The integrated intensity is probably actually greater in CCl_4.

suggests that the higher frequency carbonyl band (A) should be assigned to the *s-cis* forms of the compounds and the lower one (B) to the *s-trans* form. As one would expect the relative intensity of band A (*s-cis*) increases with the size of X. Also, the relative strength of band B is usually apparently greater in the more polar solvent.[3b, c] The ketone 3 appears to be a particularly good example. There are four well-resolved double bond stretching bands in CCl_4 and C_2Cl_4; it is tempting to assign the two outer bands to the *s-cis* form and the two inner ones to the *s-trans*.[3b] But this simple picture is complicated when one considers all the data, especially for the ketone. In this compound, the relative intensity of band A to band B is in the order $CH_3CN > CH_2Cl_2 > CHCl_3 > CCl_4$, C_2Cl_4. Similarly, a careful inspection of the ester 4 spectra indicates band B is probably actually more intense in CH_3CN. In addition, there are more than two bands in the C=C region for all the compounds.[5] The discussion below considers these facts.

In the aldehyde 1, band B is much more intense than band A and is relatively stronger in CH_3CN. Since this is the least sterically hindered compound and the *s-trans* form is electronically favored[3b], band A is assigned to $\nu_{C=O}$ (*s-cis*) and band B to $\nu_{C=O}$ (*s-trans*). The strongest C=C band, 1585 cm^{-1}, is assigned to $\nu_{C=C}$ (*s-trans*). These *s-trans* bands are near those found in the *s-trans* *mono*chlorovinyl aldehyde (1692 and 1588).[3a] The *s-cis* C=C band is probably overlaid by the *s-trans* one; both the other bands between 1500 and 1600 cm^{-1} seem too strong to go with the weak *s-cis* C=O band.

In the acid chloride **2** the two well-resolved C=O bands are of comparable intensity. The relative intensity of band B is markedly greater in CH_3CN. These two bands are therefore assigned as for the aldehyde. Both shoulders on the very strong C=C band increase as band B increases, but since it is difficult to judge intensities for these closely spaced absorptions, we are reluctant to assign any of them definitely to one conformer or the other.

The ketone **3** departs from the pattern of **1** and **2**. Bands A and B are well separated and of comparable intensity as in **2**, but the relative strength of band B *falls* with increasing solvent polarity. Both the highest and lowest band in the C=C region show the same behavior relative to the strongest C=C band. The Noack criterion, viz. that $\nu_{C=O}$ in *s-cis* shifts less than that of $\nu_{C=O}$ in *s-trans* in going from CCl_4 to $CHCl_3$[6] is no help in this case except that it may suggest that the conformers in this case are not very close to *s-cis* and *s-trans*. A quasi *s-trans* rotamer must be considerably skewed from planarity in **3** due to interference between the methyl and the nearer β-chlorine.[7] Even in *trans*-4-chloro-3-buten-2-one, the *s-trans* conformer is not quite planar[3c] and the mesityl oxide is all *s-cis*.[6] It is noteworthy that band A in **3** is at higher, and band B at lower, frequency than in the monochlorovinyl ketone under the same conditions (C_2Cl_4 solution).[3b] It thus appears that at least one of the rotamers of **3** has a different nature from those of the monochloro ketones and possibly different from those of **1** and **2**.[17] Both the slightly smaller size of chlorine compared to methyl[8] and differences in electronic structure probably account for the spectral differences between 2 and 3.

Considerations similar for those for 3 may apply to the ester 4. Changes in intensity are more difficult to gauge in 4 compared to 3, and there is a lack of data on the related monochlorovinyl compounds.[9]

Overall we conclude that the compounds studied all show rotational isomerism. The exact nature of the conformers is, however unclear, especially as X becomes larger. A recently described matrix isolation technique might help elucidate this problem.[10]

Experimental

Spectral. -- Ir spectra were taken on a Perkin-Elmer 225 Grating Infrared Spectrophotometer in 0.1 mm KBr cells. Solutions were 50 mg/ml. Nmr spectra were taken on a Varian A-60A Analytical nmr Spectrometer.

Synthetic. -- Safety note: β-chlorovinyl carbonyl compounds should be treated as vesicants. Solutions of 3,3-dichloropropenoate anion generate explosive chloroacetylene on warming.[11] The ketone 3 reacts with concentrated aqueous alkali to yield an explosive gas, probably also $HC\equiv C\text{-}Cl$.[12]

3,3-dichloropropenal 1 was obtained by a reported method:[13] bp 38-39°(21 mm); mp 2,4-dinitrophenylhydrazone 164-165° [lit.[13] bp 85°(35 mm);[14] mp 2,4-DNP 164-165°].

4,4-dichloro-3-buten-2-one 3 was prepared by acetylation of 1,1-dichloroethene[15a,b]: bp 59.5-60.0 (18 mm) [lit. bp 153-156° (atm)[15a]; 45°(10 mm), 58° (15 mm)[15b]]. This material is stable at least 8 months at -15° if carefully freed from dissolved HCl by refluxing several hours in a 30 cm Vigreux column under vacuum, distilling (90% of once-distilled material boils within a 0.5° range), and purging the main fraction with nitrogen.

3,3-dichloropropenoic acid was prepared by the haloform reaction (0-5°) on a mixture of 4,4,1-trichloro-3-buten-2-one and 4,4,4,1-tetrachloro-2-butanone, prepared analogously to 3, using ordinary chlorine bleach (55% overall yield): wh. needles from CCl_4, mp. 76-77° [lit.[16a,b] mp 76-77°]; ir (CCl_4) 1742(w, sh), 1706 (vs, C=O), 1598 cm^{-1} (vs, C=C); nmr (CCl_4) δ 6.38 (s, 1, $Cl_2C{=}C\underline{H}$), 12.21 (s, 1, $COO\underline{H}$); satisfactory analyses for C, H, and Cl.

3,3-dichloropropenoyl chloride 2 was prepared in 75-80% yield by refluxing the acid 1.5 hr with a 75% excess of $SOCl_2$ and fractionating: col. liquid, bp 51.6 - 52.2 (18 mm) [lit.[16b] bp 145° (atm)]; no $SOCl_2$ by ir.

Methyl 3,3-dichloropropenoate 4 was prepared by Fischer esterification of the acid (10% H_2SO_4 in ~ 20-fold excess CH_3OH, 2 days reflux). Fractionation after the usual work-up gave a 75-80% yield of colorless liquid, bp 57.7 - 58.8° (18 mm). This compound has mp ~ 15°; the analytical sample, whose ir spectrum was identical to that of the distillate, was obtained by fractional freezing.

Anal: Calcd. for $C_4H_4Cl_2O_2$: C, 31.00; H, 2.60. Found: C, 31.09; H, 2.61.

Footnotes

1. NSF Predoctoral Fellow, 1966-1970.
2. Our interest in these compounds stems from our discovery that they react with certain secondary amines to yield directly aminoethynyl carbonyl compounds [ethynylogous amides, "push-pull" acetylenes, cf. H. -J. Gais, K. Hafner, and M. Neuenschwander, Helv. Chim. Acta, **52**, 2641 (1969)]. These results will be communicated shortly.
3. (a) J. Terpinski and J. Dabrowski, Bull. Acad. Polon. Sci. Ser. Sci. Chim., **17**, 355 (1969).
   (b) J. Dabrowski and K. Kamienska-Trela, Bull. Chem. Soc., Japan, **39**, 2565 (1966).
   (c) J. Dabrowski and J. Terpinski, J. Org. Chem., **31**, 2159 (1966).
4. We recognize that both conformations may deviate from planarity; cf. A. J. Bowles, W. O. George, and W. F. Maddams, J. Chem. Soc., B, 810 (1969), and D. D. Faulk and A. Fry, J. Org. Chem. **35**, 365 (1970).
5. Factors other than rotational isomerism that may cause band splitting (e.g., Fermi resonance) are discussed in references 3b, c and references cited therein. See also footnote 17.
6. K. Noack, Spectrochim. Acta, **18**, 1625 (1962).
7. A sketch made to scale using reasonable values for bond lengths and contact radii (values from L. Pauling, "The Nature of the

Chemical Bond," (3rd ed.), Cornell University Press, Ithaca, N. Y., 1960), or the use of models shows this.

8. L. Pauling, *op.cit.* (note 7).
9. A. N. Kurtz, W. E. Billups, R. B. Greenlee, A. F. Hamil, and W. T. Pace, *J. Org. Chem.*, **30**, 3141 (1965) report only one C=O band for *cis* and *trans* 3-chloropropenoyl chloride and the methyl esters. However, the resolving power of their instruments was probably less than that of ours.
10. A. Krautz, T. D. Goldfarb, and C. Y. Lin, *J. Amer. Chem. Soc.*, **94**, 4022 (1972).
11. O. Wallach, *Liebigs Ann.* **203**, 83 (1880), and our observations.
12. We surmise that this occurs by a reaction analogous to the "acid" cleavage of acetoacetic esters.
13. M. S. Kharasch, O. Reinmuth, and W. A. Urry, *J. Amer. Chem. Soc.*, **69**, 1105 (1947).
14. In view of the bp's of the compounds **2** - **4**, this is almost surely a typographic error in ref. 13.
15. (a) O. Wichterle and J. Vogel, *Collec. Czech. Chem. Commun.*, **19**, 1197 (1954).

    (b) I. Heilbron, E. R. H. Jones and M. Julia, *J. Chem. Soc.*, 1430 (1949).
16. (a) F. Strauss, L. Kollek, and W. Heyn, *Ber. Dtsch. Chem. Ges*, **63**, 1868 (1930).

    (b) O. Wallach, *Liebigs Ann.* **193**, 1 (1878).

17. Note Added in Proof. After the submission of this Note, we found that we had overlooked a differing interpretation of the spectrum of the ketone 3 in the literature. Based on a film spectrum and the dipole moment of 3, S. Searles, Jr., R. A. Sanchez, R. L. Soulen, and D. G. Kundiger [*J. Org. Chem.*, **32**, 2655 (1967)] regard 3 as all *quasi* *s-trans*. They assert band B is an overtone of the strong unsplit (in their spectrum) C-Cl band at 833 cm^{-1}.

We re-examined our spectra with the following results and conclusions: In CS_2 and CCl_4 band B is more intense than the C-Cl absorption and the latter is split in CS_2 (832 and 817 cm^{-1}). There is no absorption near 785 cm^{-1}; thus the splitting of the C=C absorption cannot be due to Fermi resonance or an overtone. We believe it unlikely that *s-trans* 3 would have its C=O absorption ~20 cm^{-1} *higher* than *s-trans* 1 unless the former is highly skewed (and therefore effectively non-conjugated), a conclusion the above authors reject. The fact that *s-cis* 3 might well be *more* polar than the *s-trans* conformer, as stated by these authors, is consistent with our solvent effect data. Thus, we believe 3 to exist as two conformers, at least in solution.

None of the compounds 1, 2, or 4 has a strong absorption at one-half the frequency of the weaker carbonyl band.

PAPER II

The following manuscript has been accepted for publication in the *Journal of Organic Chemistry*.

The Reaction Product of 3,3-Dichloro-2-Methylpropenal and Piperidine

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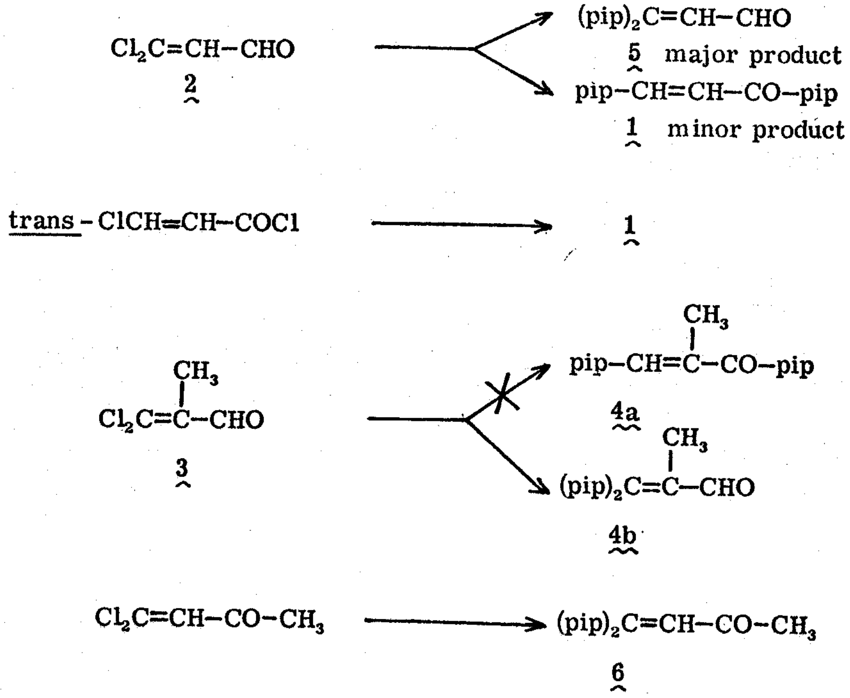
Abstract: Evidence is cited to show that the title reaction product is 3,3-bis(piperidino)-2-methylpropenal rather than 1-(2-methyl-3-(piperidino)-propenoyl)-piperidine as reported.[1]

We recently attempted to prepare the vinylogous urea 1 by reaction of 3,3-dichloropropenal (2) with piperidine. Our hope for success lay in the claim by Kundiger and Morris,[1] later mentioned in passing somewhat less definitely,[2] that 3,3-dichloro-2-methylpropenal (3) gives the 2-methyl homolog (4a) of 1 with piperidine. The authors[1] suggested initial attack of the amine on the carbonyl group as a mechanism. Since the aldehyde 2 is less hindered at the carbonyl than its homolog 3, we anticipated the formation of the desired urea 1.

We found that reaction of 2 gave a mixture of two olefins (nmr) in 70-80% crude yield. The first, (5), 85-90% of mixture, had absorptions at 4.18 δ (d, J = 7 Hz) and 9.03 δ (d, J = 7 Hz). The other, 10-15% of

Summary of Reactions[a]



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[a] pip = $C_5H_{10}N$-

mixture, absorbed at 4.91 δ (d, J = 13 Hz) and 7.14 δ (d, J = 13 Hz). Only the absorptions of the minor product are consistent with those of 1. An authentic sample of 1 prepared from *trans*-3-chloropropenoyl chloride has the same absorptions (confirmed by peak enhancement) and coupling constant, and two distinct envelopes for the α-piperidino protons centered at 3.10 and 3.37 δ.

The spectrum of the major product 5 is consistent with that expected for the formyl ketenaminal 3,3-bis(piperidino)propenal. The δ values and coupling constant are reasonable for =C$\underline{\text{H}}$–C$\underline{\text{H}}$O in this compound. The α-piperidino protons are in a single envelope for this compound.[3]

We therefore duplicated the preparation of Kundiger and Morris.[1] To avoid possible loss of a minor or more soluble isomer, we initially assayed the crude material. There was no absorption near 7 δ but a singlet at 9.0 δ and one envelope for the α-piperidino protons, centered at 3.12 δ. Work-up gave ~40% yield of a bright yellow solid with the properties reported by the above workers. The nmr spectrum of this purified material was the same as that of the crude, allowing for medium differences and minor impurities. Comparison of this spectrum with those of the aminal 5 and the vinylogous urea 1 strongly suggests compound 4 is the formyl ketenaminal 4b rather than the vinylogous urea 4a.

Support for our structure assignment for 4 is found in the nmr spectrum of the isomeric acetyl ketenaminal 6. This aminal 6 has α-piperidino proton absorptions in a single envelope, like 4 and 5 and unlike 1.

We conclude therefore that the title product is in fact 3,3-bis (piperidino)-2-methylpropenal (4b). None of the evidence cited by the original workers[1] excludes this structure. Thus, 4b as a *vinylidenolog*[4] of a formamide can base hydrolyze to give two equivalents of piperidine; the other hydrolysis product, 2-formyl propionic acid would be the same from 4a or 4b. The low carbonyl stretching frequency is consistent with either structure; our comparative data in dilute CCl_4 give bands at 1616 cm^{-1} for 4b, 1627 cm^{-1} for the isomeric acetyl ketenaminal 6 and 1640 cm^{-1} for 1.

The small amount of 1 formed from 2 may be from initial attack at the carbonyl[1] or by the rearrangement of the possible intermediate 3-chloro-3-(piperidino)propenal to 1-(3-chloropropenoyl)piperidine[5] and aminolysis of this vinylogous carbamyl chloride.

Experimental

Caution: -- β-chlorovinyl carbonyl compounds exhibit mustard gas-like vesicatory action. The aldehyde 2 and 4,4-dichloro-3-buten-2-one are cleaved by concentrated aqueous alkali to explosive chloroacetylene. All the dihalides can be safely destroyed by slow addition to excess aqueous ammonia.

General Synthetic Procedure. -- Essentially the procedure of Kundiger and Morris was followed.[1] The dihalides were added dropwise with stirring at 0°-5° to 6-8 molar equivalents of piperidine in ether or benzene and stirred at room temperature for 1-2 days. The piperidine hydrochloride was filtered off and washed thoroughly with ether (90-100%

yield), and the ether solution stripped on a rotary evaporator (50-60°/13 mm). If any solid appeared and then redissolved (piperidine hydrochloride) or an amine odor remained, the material was taken up in hot methylcyclohexane, filtered, and re-stripped.

When stored in sealed vials, compounds **1**, **4b**, and **6** discolor slowly. However, decomposition was very slow when these compounds were stored in *open* vessels over KOH $|H_2SO_4|$ paraffin shavings in a desiccator protected from light at room temperature.

Reaction of 3,3-Dichloropropenal (2). -- The starting material was prepared as reported.[6]

Following the general procedure 2.50 g (20 mmol) **2** in 50 ml ether was allowed to react with 15 ml (~ 150 mmol) piperidine in 100 ml ether. Work-up afforded 3.37 g (76%) of an orange oil, which was ~ 7:1 mixture of **5** and **1**. Nmr (CCl_4) δ 1.62 (broad and unresolved, all 12 β- and γ-piperidino H's in both products), ~ 3.18 (broad and distorted multiplet, all eight α-piperidino H's in both products), 4.18 (d, J = 7 Hz, α-vinyl H in **5**), 4.91 (d, J = 13 Hz, α-vinyl H in **1**), 7.14 (d, J = 13 Hz, β-vinyl H in **1**), 9.03 (d, J = 7 Hz, formyl H in **5**). The absorptions at 4.91 and 7.14 δ were enhanced on addition of authentic **1** to the mixture.

1-(3-(piperidino)-propenoyl)-piperidine (1). -- Distillation of 48.0 g (450 mmol) *trans*-3-chloropropenoic acid[7a] with 82 ml (710 mmol) benzoyl chloride through a 30 cm Vigreux column keeping the head temperature below 116°[7b] afforded 32.6 g (58%) *trans*-3-chloropropenoyl chloride, bp 107-116 (748 mm) [lit.[7a] bp 115-115.5 (atm)]; nmr (neat) δ 6.22 (d, 1, J = 13 Hz, α-H), 7.32 (d, 1, J = 13 Hz, β-H). This material contained some dissolved HCl and a little benzoyl chloride but was not further purified.

Following the general procedure, 12.5 g (100 mmol) of the acid chloride in 30 ml ether was allowed to react with 60 ml (600 mmol) piperidine in 350 ml ether. Work-up gave 19.3 g (87%) crude yellow product. Two recrystallizations from ethyl acetate afforded slightly stained material, mp 98.5 - 99.5. Two further recrystallizations gave near white needles: mp 99-100°; ir (CCl_4) 1640 (s, C=O), 1572 cm^{-1} (s, C=C); nmr (CCl_4) δ 1.57 (broad, 12, β- and γ-piperidino H's), 3.10 and 3.37 (two distorted multiplets cleanly separated, 4 each, α-piperidino H's), 4.89 (d, 1, J = 13 Hz, α-vinyl H), 7.11 (d, 1, J = 13 Hz, β-vinyl H).

Anal: Calcd. for $C_{13}H_{22}N_2O$: C, 70.23; H, 9.97; N, 12.60
Found: C, 70.06; H, 10.01; N, 12.44.

3,3-Bis(piperidino)-2-methylpropenal (4b). In 40 ml ether 7.0 g (50 mmol) of the aldehyde 3[1] was allowed to react with 35 ml (350 mmol) piperidine in 200 ml ether in the usual way to give 8.71 g (74%) crude yellow-orange solid. The reported work-up[1] and repeated recrystallization from ethyl acetate and cyclohexane gave yellow needles of 4b; mp 127-129° [lit.[1] mp 129-131°]; nmr (CCl_4) δ 1.47 (s, CH_3), 1.59 (broad, β- and γ-piperidino H's, base overlaps δ 1.47, total both 15), 3.12 (distorted poorly resolved multiplet but one envelope, 8, α-piperidino H's), 8.97 (s, 1, CHO); ir (CCl_4) 2853 (m) 2819 (m, sh) 2727 (w, sh) (possibly formyl C—H)[8], 1616 (s, C=O), 1541 cm^{-1} (vs, C=C); ir (Nujol) 1604, 1535-1520 cm^{-1} [lit.[1] 1608, 1527 cm^{-1}].

4,4-bis(piperidino)-3-buten-2-one (6). -- 4,4-dichloro-3-buten-2-one was prepared as previously described (Darzens/Friedel-Crafts acetylation of 1,1-dichloroethene)[9a,b] except that substitution of dichloromethane for carbon tetrachloride as solvent facilitates stirring.

The general procedure, using 13.9 g (100 mmol) of the dichlorovinyl ketone in 25 ml benzene and 65 ml (650 mmol) amine in 180 ml of the same solvent, gave 21.8 g (92%) crude yellowish product.[10] Two recrystallizations from ethyl acetate gave 14.5 g (61%) near white crystals, mp 79.5 - 80.5° [lit.[11] mp 80-81°]. Re-work of the mother liquors ultimately gave a total of 19.3 g (82%) of material with mp $>$ 78°. Ir (CCl_4) 1627 (s, C=O), 1501 (s, C=C) cm^{-1}; ir (Nujol) 1617, 1508 cm^{-1} [lit.[11] 1623, 1517 cm^{-1}]; nmr (CCl_4) δ 1.56 (broad, 12, β- and γ-piperidino H's), 1.80 (s, 3, methyl), 3.07 (broad and distorted but one envelope, 8, α-piperidino H's), 4.23 (s, 1, vinyl H); nmr ($CDCl_3$) δ 1.60, 1.96, 3.17, 4.40 [lit.[11] δ 1.60, 1.98, 3.19, 4.41]. This compound has an anise odor not abolished when stored several months as described above.

Acknowledgment

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3. Acyl ketenaminals typically have low barriers to rotation about the carbon-carbon double bond and have their α-amino proton absorptions isosynchronous or nearly so: [J. Sandström and I. Wennerbeck, *Chem. Commun.*, 1088 (1971), and E. Ericsson, J. Sandström, and I. Wennerbeck, *Acta. Chem. Scand.*, **24**, 3102 (1970), and refs. cited therein]. We have found 4,4-bis(dimethylamino)-3-buten-2-one to have a single sharp absorption for all four N-methyls at 38° with only slight broadening at -70° in ether.

4. Name adopted to describe the relationship between e.g., RCOX and $RCO{-}\overset{|}{C}{=}CX_2$, as does *vinylog* for $RCO{-}\overset{|}{C}{=}\overset{|}{C}X$, and *ethynylog*, for $RCO{-}C{\equiv}C{-}X$ [latter due to K. Hafner and M. Neuenschwander, *Angew. Chem.*, Internat. Edit., **7**, 459 (1968)]. A referee has noted that *vinylidenolog* does not distinguish $XCH{=}C(CHO)_2$ from $X_2C{=}CHCHO$.

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8. L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," (2nd ed.), John Wiley and Sons, Inc., New York, 1958, p. 157.
9. (a) S. Searles, Jr., R. A. Sanchez, R. L. Soulen, and D. G. Kundiger, *J. Org. Chem.*, **32**, 2655 (1967); (b) J. B. Ellern and H. B. Gray, *J. Org. Chem.*, **37**, 4485 (1972).
10. The acetylene, 4-(piperidino)-3-butyn-2-one is an intermediate (ir). Use of too little piperidine permits this intermediate to decompose to red-brown polymeric material. If diethylamine is substituted for piperidine, addition of excess amine to the corresponding acetylene is is so slow that it can be isolated in > 75% yield. These results will be presented in detail in a future article.
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PART II

COBALT(II) CHLORIDE COMPLEXES OF TERTIARY VINYLOGOUS AMIDES AND RELATED LIGANDS

Introduction

The original intent of my graduate study was to prepare some of the compounds described in Part I of this thesis and attempt their binding to transition metal ions. During the work, I became rather enamored of the purely organic part, especially that of Part I, Chapter 2. Accordingly, my efforts were diverted from the original purpose. Hence, the results set forth in this part of this thesis constitute for most of the compounds described only a partial characterization.

This study differs from the usual investigation of the reactions of new ligands. Typically, an inorganic chemist with a new potential ligand in hand attempts to prepare and characterize complexes with just that ligand and a variety of metals. This work took the opposite tack. Having discovered shortly after the preparation of the vinylogous amide 11 that it reacted readily only with cobalt(II) chloride (37) among the readily available divalent transition metal salts, I pursued the study of its interaction with some of the compounds of Part I, thus keeping the metal substrate constant and varying the ligand.

The species studied all showed certain similarities. With few exceptions, differences among them were more of degree than of kind, as I interpret the experimental results. Therefore, this Part consists of a single chapter to lend coherence to the presentation of the various aspects of the species which were studied.

Background

To my knowledge, vinylogous amides* with a tertiary nitrogen have not been employed as ligands for metals. While complexes of the monoanions of primary and secondary simply vinylogous amides have been extensively explored and good preparative methods worked out,[132] these ligands differ fundamentally from the compounds with a tertiary nitrogen in that the latter lack an acidic hydrogen.

The title ligands would be expected to behave somewhat like the compounds of which they are vinylogs, viz., tertiary amides. Many complexes of the latter have been prepared and characterized.[133-140] The general mode of preparation involves treating an inorganic salt, usually anhydrous or dehydrated in situ, with a large excess of amide and precipitation of the complex by addition of ether or a similar solvent. The complexes display a variety of stoichiometries and steric dispositions of the ligands about the central metal. A common characteristic of these species is the appearance of a lower carbonyl stretching frequency in their infrared spectra than in the unbound ligand.[133-139] This has been inferred to indicate that amides are bound to the metal through oxygen rather than nitrogen,[141] although the possibility of dynamic ligation with weak N-binding has been raised.[137]

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* Throughout this Part, "vinylogous amide" includes ethynylogous and vinylidenologous amides, unless otherwise stated.

Another ligand to which vinylogous amides could be similar in forming complexes is acetylacetone (10) as a *neutral* ligand. However, the complex of 37 with 10 has been found to have 10 acting as a chelate in its diketo form.[142] Since my ligands are locked in the enamine (or ynamine) form, behavior strictly analogous to that of neutral 10 cannot occur.

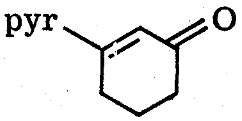
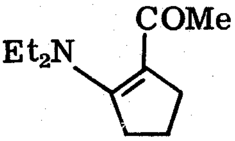
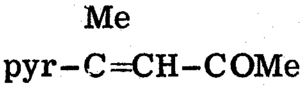
The work just cited, especially that on amide complexes, gave me only a vague idea of what to expect from complexation of 37 with my ligands. The situation with the vinylogous amides involves not only the possibility of N- or O-coordination. As noted in Part I, other complications are interaction of 37 with the polarized carbon-carbon multiple bond, variable ligand stereochemistry, and the possibility of chelation with a ligand for which a *cis*,*s*-*cis* configuration is mandatory or possible. However, some of the synthetic methods and spectral correlations applicable to amide complexes were found to be useful.

Syntheses

The species listed in Table II were prepared. Complexes 38, 40, 41, and 43 were obtained as intense blue or blue-green solids; 40 and 41 analyzed ~ 5-10% high in ligand. Compounds 39 and 42 were obtained only in solution. Similarly, 44 and 45 were not obtained crystalline, but because the very strong C≡C ir absorption of the uncomplexes ligands is absent in the complexes, their stoichiometry could be established by titration. That complex formation occurs between 37 and vinylogous amides in general was shown by

Table II

List of Complexes of $CoCl_2$

Compound No.	Ligand and Stoichiometry
38	2  1
39	x  2
40	$2\ Me_2N-CH=CH-COMe$ 3
41	2  $\text{pyr}-\overset{\text{Me}}{\text{C}}=\text{CH}-\text{COMe}$ 13
42	x pip–CH=CH–CO–pip 16
43	$2\ (\text{pip})_2C=CH-COMe$ 33
44	$1\ Et_2N-C\equiv C-COMe$ 32
45	$1\ (Me_2CH)_2N-C\equiv C-CN$ 36

the uptake of 37 into even dilute ligand solutions in polar chlorinated organic solvents.

This last fact was basis for the most generally applicable method of preparing the complexes. Typically, 37 was slurried in DCE or CH_2Cl_2, and after addition of the ligand, the mixture was shaken or stirred. The blue or green solution was then filtered from undissolved 37, and the complex precipitated either by merely letting the solution stand stoppered (40 and 41) or by addition of benzene or toluene and evaporation.

The rationale behind this synthetic method is as follows: The salt 37 is insoluble in DCE or CH_2Cl_2; hence the filtered solution cannot contain any uncomplexed 37. The ligands are all soluble in benzene and toluene, and therefore complexes precipitated as described should be free of excess ligand. To obtain solids as opposed to thick oils, slow precipitation was sometimes necessary. This was accomplished by always using a poor solvent for the complexes less volatile than the chlorinated solvent in which they were made; evaporation then slowly enriched the solution in the poor solvent.

The rate at which 37 dissolved in DCE/ligand solutions varied with the ligand. With the ligands 1, 3, 13, 16, and 33, uptake of 37 was fast. After only a few minutes agitation with excess 37, filtered solutions showed little to no uncomplexed ligand by ir, i.e. reaction was essentially complete. With the ligands 2, 32, and 36, reaction was usually slower. The complexes of these last three ligands and of 16 could not be gotten as solids, forming only oils or obviously contaminated semi-solid materials despite various efforts to induce crystallization. Similar difficulties have been had with some amide complexes.[136] The peculiar fact of the crystallization of the complexes 40 and 41 from the filtered DCE solutions *without* addition of a poor solvent or reduction of solution volume will be discussed below.

One other synthetic method useful for some of the complexes was addition of the ligand to the hexahydrate of 37 after dehydration with DMP.[143] Provided less than ~ 150% excess DMP is used for the dehydration, finely ground 37 hexahydrate dissolves on stirring with DMP to a deep blue solution. This dissolution must be because hydrolysis of DMP generates acetone and methanol (in which 37 is soluble) since 37 is not soluble in DMP alone. Addition of ligand to this *in situ* generated solution of 37 always gave evidence of reaction, either by color change or intensification of blue color of the solution. From the ligand 1, the complex 38 precipitated directly as a solid. With the ligands 2 and 32, green oils separated, which could not be solidified. With the ligand 3, blue semi-solid formed, which partially solidified on trituration with more DMP. In no case was the method superior to the previously described uptake method. Its only advantage was that where solid complexes could be obtained directly, it avoids the necessity of advance preparation of the very hygroscopic 37.

Properties of the Complexes and Discussion

Certain casually evidence properties of the complexes are worth noting initially. All those obtained as crystalline solids had melting points substantially above that of the corresponding ligand and intense blue to blue-green colors; the complexes 39 and 44 were obtained only as very viscous green oils. The solids, 38, 40, 41, and 43, and the oil 44 are very much less hygroscopic than the starting salt 37 and do not decompose nearly so rapidly on exposure to ambient air as do the ligands from which they are made. A sample of 38 in an open beaker on a shelf discolored only slightly and changed weight by less than 0.5% over 8 months. A CH_2Cl_2 solution of 44 allowed to evaporate in the open air became a green gum which then remained visibly unaltered for two years and still showed the cycling color changes with different solvents, discussed below. The complex 39 was less stable than the others. In solution, it became brownish and deposited brown gunk after a few days. When obtained as very viscous green oil by prolonged pumping on it, it still underwent similar but slower decomposition even at 0-5°.

Though not very hygroscopic, the complexes were all destroyed by water. When the ligand 13 was added to an aqueous solution of 37 hexahydrate, a deep blue color appeared which faded as $Co(acac)_2(H_2O)_2$ precipitated as orange needles (identified by its ir spectrum[144]). Solutions of the complexes in polar chlorinated solvents or MeCN were intense blue (38, 40-43) or green (39, 44, 45), changing instantly from blue to pale magenta or from green to yellow on addition of methanol (green to pink for 39) and back again on further addition of either DCE or MeCN. This color cycling could also be done in the reverse order, i.e. by initial dissolution in methanol. The salt 37 gives the pink-blue conversion but is not soluble in DCE or CH_2Cl_2.

Visible and infrared spectral data for the complexes are set forth in Tables III and IV. These data will be discussed first for the complexes of the polarized ethylenes and separately for those of the acetylenes.

The complexes 38-43 have visible spectra consistent with tetrahedrally coordinated cobalt(II).[145a,b,c] All are solvolyzed to at least some extent by MeCN, showing absorptions which differ from that of the complexes in DCE and usually from that of 37 in MeCN. The salt 37 itself has a complicated monomer-dimer equilibrium in MeCN involving ionic species and coordinated solvent.[146] My data show, however, that except for the complex 45, the ligands are still affecting the visible absorption spectrum of the cobalt(II) and the cobalt(II) is usually influencing the multiple bond stretching frequencies of the ligands, even though an overwhelming concentration of MeCN is present.

Consideration of the complexes individually is appropriate here. The complex 38 has both multiple bond stretching frequencies at lower frequency than in the unbound ligand. Thus, O-bonding to the metal inferred by analogy to amide complexes,[133,136,137,140] although some interaction with the α-carbon cannot be ruled out. This compound was a non-conductor in CH_2Cl_2 as are amide complexes of the cobalt(II)

Table III

Visible Spectra of Complexes of $CoCl_2$

Species	Solvent	Absorptions in nm (ϵ)
$CoCl_2$ (37)	MeCN	682 (419), 613 (259), 585 (227), 571 (262)
38	DCE	657 (922), 631 (778), 602 (576)
38	MeCN	668 (639), 572 (328)
39	DCE[a]	668 (360)
39	MeCN[a, b]	682 (314), 578 (120)
40	MeCN	671 (565), 621 (352), 572 (324)
37 + 2.1 3	MeCN[b]	672 (458), 619 (318), 572 (281)
37 + 2.1 3	DCE[b]	659 (682), 599 (419)
41	MeCN	678 (714), 584 (375)
37 + 2.2 13	MeCN[b]	670 (588), 570 (275)
37 + 2.2 13	DCE	662 (732), 607 (406)
42[a]	DCE[b]	677 (372), 655 (342)
42[a]	MeCN[b]	679 (382), 587 (182)
43	DCE	670 (613), 634 (488), 605 (351)

Table III (Continued)

Species	Solvent	Absorptions in nm (ϵ)
43	MeCN	675 (464), 590 (292)
44[a]	MeCN[b]	685 (302), 585 (222)
45[a]	MeCN[b]	680 (427), 613 (274), 585 (255), 570 (280)

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[a] With excess ligand.

[b] Made up in solution and spectrum measured immediately.

Table IV

Infrared Spectra of Complexes of $CoCl_2$, 2000-1450 cm^{-1}

		Absorptions (cm^{-1})	
Species	Solvent	Complex	Ligand Alone
38	DCE	1566(m), 1515(vs)	1606(s), 1555(s)
39	DCE	1711(s), 1588(s)	1622(vs), 1525(vs)
40	Nujol mull	1630(brd), 1535(brd)	--
40	MeCN	1657(m), 1628(vs), 1606(s), 1572(s)	1659(s), 1628(s), 1604(vs), 1656(vs)
37 + 3[a]	DCE	1633(vs), 1567(s), 1518(vs, brd)	1658(s), 1628(m-s) 1606(vs), 1569(vs)
41	Nujol mull	1655(w), 1565(brd)	--
41	MeCN	1623(m), 1519(vs)	1623(s), 1522(vs)
37 + 13[b]	MeCN	1566(s), 1508(vs)	1623(s), 1522(vs)
37 + 13[a]	DCE	1567(s), 1509(vs)	1626(s), 1533(vs)
42[a]	DCE	1626(vs), 1599(s)	1638(vs), 1565(s)
43	DCE	1717(w), 1599(m), 1540(s, sh), 1516(vs), 1494(vs)	1612(s), 1496(vs)

Table IV (Continued)

Species	Solvent	Absorptions (cm^{-1})	
		Complex	Ligand Alone
44	DCE	1653(s), 1631(s), 1573(s), 1556(s)	2155(vs), 1627(s)
44	MeCN	1712(m), 1656(s), 1625(s), 1590(vs)	2155(vs), 1630(s)
45	DCE	1656(s), 1584(vs)[a, c]	2125(vs), 2133(s)
45	THF	1661(s), 1580(vs)[c]	2126(vs), 2134(s)
45	MeCN	1712(w), 1650(s), 1593(vs), 1547(s)	2125(vs), 2132(s)

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[a] Excess $CoCl_2$ shaken with ligand solution, filtered, and spectrum of filtrate measured immediately.

[b] Excess $CoCl_2$ present.

[c] Reaction incomplete; absorptions of uncomplexed ligand also appeared in spectrum.

halides.[136,147] The visible spectrum in MeCN implies some solvolysis, but in the solid and in non-coordinating solvents, formulation as CoL_2Cl_2 satisfactorily explain its properties.

The species **39**, though poorly characterized, clearly exhibits a different mode of binding than **38**. Both ligand multiple bond stretching absorptions are at *higher* frequency than those of the free ligand. This implies N-bonding, or at least that the cobalt is not interacting with the ligand such as to lower the primarily C=O stretching frequency. A strictly planar enamino ketone configuration is probably not possible for the ligand **2** since it has both α- and β-alkyl substituents.[23b] The fact that of all the polarized ethylene ligands studied, **2** is the most sterically crowded and is the only one *cis*-constrained probably accounts for its different mode of binding. Chelation of the metal by **2** is possible, but it is unlikely that chelating **2** would have a stretching frequency at approximately that of an uncomplexed saturated ketone.[17] However, the only definite assertion about **39** that can be made on the bases of my data is that the binding is very different from that of the other polarized ethylenes.

The complexes **40** and **41** of the open-chain ligands, **3** and **13**, respectively, have a DCE-soluble and DCE-insoluble form. In case of **40**, both forms were isolated and had the same stoichiometry, $CoCl_2 \cdot 2L$. Although analyzing somewhat high in ligand, **40** and **41** did not approach fitting $[CoL_6][CoCl_4]$ found for the complex of **37** with

N-methylbutyrolactam[135] which requires $CoCl_2 \cdot 3L$ and shows the electronic spectrum of $CoCl_4^=$,[145c] which 40 and 41 do not.

The ir spectra of DCE-insoluble 40 and 41 in Nujol are so poorly defined as to permit no structural conclusions other than to note that the spectra are different from those of the free ligands, neat or in saturated hydrocarbons.[23a] The ir spectra of the solids dissolved in MeCN show only unbound ligand, although the visible spectra are somewhat different from those of just 37 in MeCN with no ligand present.

The ir spectrum of DCE-soluble 40 is indicative of principally O-bound ligand on the same basis as for 38 above, although the frequency shift is less. Since the ligand 3 is the one with the greatest amount of steric freedom (cf. Part I), a mobile mode of ligation would not be surprising, especially in solution.

With the complex 41, the situation is more like that of 38. The infrared spectra measured rapidly after making up the complex in either MeCN or DCE are the same. In both solvents, there is a marked decrease in the higher frequency ligand absorption from that of the free ligand.

The fact that the ligand 3 and 13 take up 37 into DCE and then slowly spontaneously deposit DCE-insoluble 40 and 41 from the solutions is the most peculiar aspect of these systems' behavior. There is obviously a rapidly formed complex which undergoes some kind of isomerization to a more stable one. The process could involve a combination of ligand and coordination isomerization. With respect to the latter possibility, it should be noted that CoL_2Cl_2 and oligomers thereof and $[CoL_nCl_{4-n}][CoL_{4-n}Cl_n]$ (n = 3 or 4) all have the same stoichiometry. My attempts to obtain conductivity data on 40 and 41 were totally frustrating. The bridge could not be balanced; possibily the complex and/or ligand were adsorbed on the electrodes.

The complex 42 was not obtained as a solid. Unlike 40 and 41, it did not crystallize spontaneously from DCE solutions. Its noteworthy spectral feature was that the ligand multiple bond absorptions move closer together in the complex compared to the free ligand and in opposite directions. This suggests a mode of ligation which tends to equalize the bond orders, possibly metal interaction with the whole conjugated system of the ligand 16 running from the enamine nitrogen through the amide carbonyl.

The complex 43 of the *bis*(β-amino)enone 33 was an intense blue solid, always totally soluble in DCE, and giving an excellent analysis for $CoCl_2 \cdot 2L$. The multiplicity of ir absorptions is indicative of a mobile mode of binding of the ligand to the metal. The osmometrically determined molecular weight of 380 in chloroform shows dissociation of the complex (formula weight for CoL_2Cl_2 is 602.6), proving that dissociation occurs in this solvent. The value of 380 does not fit any single obvious dissociation process. The simplest one, *viz.*, partial dissociation of one organic ligand with the one remaining bound chelating, is hard to reconcile with the fact that $CoCl_2 \cdot 2L$ precipitates cleanly from DCE/toluene in the absence of excess ligand. The dissociation probably involves ionic species, of the types mentioned above in connection with the complexes 40 and 41.

The complexes 44 and 45 of the acetylenes 32 and 36 were somewhat different from those of the olefins. I initially thought that complexation with 37 might have involved a definite change in the oxidation state of the metal. But the rapid color cycling with solvent change makes cobalt(III) unlikely (substitution inert), and the visible spectra is not compatible with this oxidation state.[148a,b] In fact, the visible spectrum of 45 MeCN is nearly identical to that of 37 in the same solvent. The yellow color of 44 and 45 in methanol was found to be due merely to a tail from a ligand or charge transfer band in the ultraviolet (maximum not located).

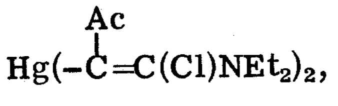
The few known tetrahedral cobalt(I) complexes have visible spectra somewhat similar to those of tetrahedral cobalt(II).[149] But the former are readily oxidized in solution,[149] whereas 44 and 45 are not. The above comment about the visible spectrum of 45 in MeCN also bears on this question.

The striking feature of the species 44 and 45 is the abolition of the acetylenic absorption on complexation of the ligand 32 to form 44 and of both triple bond absorptions of 36 on conversion to 45. The fact that the stoichiometry of both complexes is one $CoCl_2$ to one ligand implies that both ligands are acting as four electron donors to the cobalt, assuming that all the cobalt is four-coordinate. The visible spectrum of 45 in MeCN is troubling in this respect since it is so nearly identical to that of $CoCl_2$ itself. It may be simply that the bound ligand is in a feebly absorbing metal moiety; a similar comment applies to the species 44, whose visible spectrum is also not very different from that of the starting material 37.

The infrared spectra however leave no doubt that the acetylenic ligands have been profoundly altered by the salt 37. That this is not simply a catalytic process was shown by the titrations to establish the stoichiometry. On adding the ligands little by little to 37 in MeCN and immediately determining the ir spectra, it was found that the triple bond absorptions disappeared until the ligand:$CoCl_2$ ratio reached 1:1 after which the spectrum of the uncomplexed ligand persisted.

Unfortunately, attempts to decompose the complexes to find out if the ligands reappeared unchanged were inconclusive. Iodination of the complexes, a method which has been used to decompose alkyne complexes,[150] gave only intractable tar. Treatment with water decomposed the complexes, but no organic product could be recovered.

Two control experiments with different metals were run using the ligand 32. Lithium chloride had no effect on the ir spectrum of 32 in THF. On the other hand, mercury (II) chloride formed a complex $HgCl_2 \cdot 2L$ in THF in which the acetylenic absorption was absent. The addition of mercuric salts across carbon-carbon multiple bonds is a well-known reaction[151]; it is easy to believe that $HgCl_2$ reaction with 32 gives a species with a structure such as



$Hg(-\overset{\overset{\displaystyle Ac}{|}}{C}{=}C(Cl)NEt_2)_2$,

possibly with the chloride dissociated.

Thus, the question of even the molecular structure of the complexes is unresolved. If the bound ligands 32 and 36 are essentially intact, i.e. have not rearranged or undergone some covalt bond forming reaction, interaction of the metal with the triple bonds must be quite strong. If, as seems probable, this interaction involves a π-bonding interaction, agonizing about the formal oxidation state of the cobalt is pointless.

An intriguing possibility is that the acetylenes have undergone a carbon-carbon bond forming reaction induced by 37 and that the product(s) is bound to the metal. Numerous alkynes are oligerimerized by transition metals.[152] "Push-pull" acetylenes afford relatively stable cyclobutadienes with certain acids,[115] as noted in Part I; it is conceivable that 37 acting as a Lewis acid could induce a similar reaction and then remain bound to the product.

Summary and Prospectus

The results described in this part of this thesis have, like most preliminary characterizations of new species, raised far more questions than they have answered. Even in interaction with only the single metal salt 37, the polarized olefins and acetylenes show a rich and varied coordination chemistry. Further study of the coordination behavior of these now reasonably accessible ligands is certainly warranted.

Suggestions for extension of the work described above are appended hereto as Proposition V.

Experimental

Spectra. Infrared spectra were measured as for Part I. Visible spectra were taken on a Cary 14 recording spectrophotometer in 1 cm cells. The spectral data are in Tables III and IV.

General Synthetic Procedure. For preparative scale reactions, anhydrous cobalt(II) chloride (37) was slurried in barium oxide dried CH_2Cl_2 or DCE which had stood over molecular sieves, and the ligand added. The mixture was agitated; when uptake of the inorganic material ceased, the solution was filtered. The complex was precipitated by addition of benzene (for CH_2Cl_2 solutions) or toluene (for DCE solutions) and evaporation in a stream of nitrogen, or by allowing the DCE solution to stand stoppered for several days.

The complexes obtained as solids underwent no visible change over several years in sample bottles except that DCE-soluble 40 became less soluble and slightly greener.

Anhydrous cobalt(II) chloride (37). This compound was obtained by dehydrating the finely ground hexahydrate with $SOCl_2$.[153] Gas evolution was very vigorous; the reaction was quite endothermic. Prepared this way, 37 was a very fine free-flowing blue powder, which was stored over KOH. It was extremely hygroscopic and totally soluble in water, MeOH, EtOH, and acetone.

Anhydrous 37 prepared by merely heating the hexahydrate in a 110° oven was successfully used in some preparations. It was generally less reactive than $SOCl_2$-dehydrated material and was not totally soluble in water or other solvents.

Complex of 37 with 3-N-pyrrolidino-2-cyclohexenone (38). Following the general procedure, 2.8 g (21.5 mmol) 37 was stirred with 6.7 g (40.5 mmol) ligand 1 in 50 ml CH_2Cl_2. After filtration and addition of 40 ml benzene, evaporation gave 7.9 g (86%) blue solid. Two recrystallizations from CH_2Cl_2/benzene and air drying to constant weight of finely ground solid gave material of mp 189-192°. Anal. Calcd for $CoCl_2 \cdot 2L$, $C_{20}H_{30}N_2O_2CoCl_2$: C, 52.18; H, 6.56; N, 6.09; Cl, 15.41; Co, 12.80. Found: C, 51.17; H, 6.50; N, 5.87; Cl, 16.12; Co, 13.00.

Complex of 37 with 1-acetyl-2-diethylaminocyclopentene (39).

The general procedure gave only green oils, as did reaction of 37 in DMP/MeOH/Me_2CO from DMP-dehydration of 37 hexahydrate. Attempts to cause solidification by pumping on the oils or by trituration under benzene or ether failed, giving eventually brownish gum. The DCE solution for the ir measurement was made by stirring 0.2 g ligand 2 with 0.33 g 37 in 4 ml DCE for 20 hours.

Complex of 37 with 4-dimethylamino-3-buten-2-one (40).

"Soluble form." The general procedure was followed using 2.6 g (20 mmol) 37 and 2.3 g (20 mmol) ligand 3 in 100 ml CH_2Cl_2. After filtration, 60 ml benzene was added to the filtrate, and the solution rapidly evaporated in a stream of N_2. Rapid recrystallization from CH_2Cl_2/benzene twice, filtering off a little CH_2Cl_2-insoluble material, gave 2.7 g (38%) deep blue solid, which on storage slowly became somewhat greenish and less soluble in DCE or CH_2Cl_2.

Anal. Calcd for $CoCl_2 \cdot 2L$, $C_{12}H_{22}N_2O_2Cl_2Co$: C, 40.47; H, 6.23; N, 7.87; Cl, 19.91; Co, 16.55. Found: C, 40.00; H, 6.09; N, 7.65; Cl, 20.08; Co, 16.04.

"Insoluble form." The general procedure was employed, using 1.45 g (11 mmol) 37 and 2.38 g (21 mmol) ligand 3 in 20 ml DCE. After 15 min stirring, the very deep blue solution was filtered, and the filtrate allowed to stand stoppered. After 12 hr, the solution was decanted from adherent blue-green platelets. These were scraped out, triturated under DCE, and washed several times by decantation with DCE, leaving after brief air drying, 0.70 g (9.8%) blue-green powder, mp 138-140.5.

Anal. Found: C, 39.82; H, 6.15; N, 7.59; Cl, 18.95; Co, 15.65. These values are low in *all* elements analyzed for. The ratios fit $CoCl_2 \cdot 2.1$ L.

The filtrate from the above material continued to deposit a little more blue-green solid on long standing.

Complex of 37 with 4-N-pyrrolidino-3-penten-2-one (41). Using the same procedure as for 40, 1.46 g (11 mol) 37 and 3.06 g (20 mmol) ligand 13 in 20 ml DCE gave 1.05 g (12%) blue-green powder, mp 174-177.5.

Anal. Calcd for $C_{18}H_{30}N_2O_2Cl_2Co$: C, 49.55; H, 6.93; N, 6.42; Cl, 16.25; Co, 13.51. Found: C, 49.88; H, 6.93; N, 6.02; Cl, 14.88; Co, 12.25. These values fit $CoCl_2 \cdot 2.2$ L.

Complex of 37 with 1-(3-(N-piperidino)-propenoyl)-piperidine (42). In the usual way, 1.40 g (11 mmol) 37 and 0.92 g (4 mmol) ligand 16 were allowed to react in 12 ml DCE. Uptake of 37 was rapid, but only semi-solid blue-green material was obtained on addition of toluene and evaporation of the filtered DCE solution. A solution prepared in this way was used for the ir measurement in DCE.

Complex of 37 with 4,4-bis(N-piperidino)-3-buten-2-one (43). From 1.40 g (11 mmol) 37 and 2.36 g (10 mmol) ligand 33 in 20 ml CH_2Cl_2 was obtained after evaporation of the filtered solution to which benzene had been added, intense blue solid. Trituration with benzene and air drying afforded 3.82 g (63%) 43 as a blue powder, mp 195-197°.

Anal. Calcd for $CoCl_2 \cdot 2L$, $C_{28}H_{48}N_4O_2Cl_2Co$: C, 55.81; H, 8.03; N, 9.30; Cl, 11.77; Co, 9.78. Found: C, 55.90; H, 7.96; N, 9.17; Cl, 11.90; Co, 9.64. Osmometric mol wt in $CHCl_3$ 380 (calcd. for formula wt 602.56).

Complex of 37 with 4-diethylamino-3-butyn-2-one (44). The general procedure was used, employing 0.80 g (6.1 mmol) 37 and 0.40 g (2.9 mmol) ligand 32 in 8 ml DCE. Stirring for 24 hr was required to effect abolition of the 2155 cm^{-1} absorption from the ir spectrum of the supermate. Attempts to obtain solid from the green filtrate of this mixture were unsuccessful. Methods tried include stripping, evaporation after adding toluene, and slow diffusion of ether, toluene or benzene into the solution of the complex.

Reaction of 37 and 32 was somewhat faster using THF as solvent; the salt 37 is slightly soluble in THF.

For the titration to establish the stoichiometry of the complex 44, 130 mg (1.0 mmol) 37 was dissolved in 8 ml MeCN. The ligand 32 was added little by little with frequent measuring of the ir spectrum of the solution. The 2155 cm^{-1} absorption due to uncomplexed 32 was absent until $>$140 mg (1.0 mmol) 32 had been added, after which it increased in intensity and persisted.

*Complex of **37** with 3-Diisopropylaminopropynonitrile (**45**).* The reaction between **37** and the ligand **36** were performed as for the complex **44**; reaction was generally slower than for **44**.

In a typical run, 260 mg (2 mmol) **37** in 6 ml MeCN was allowed to react with 300 mg (2 mmol) ligand **36**. After standing ~ 2 hr, the strong ligand absorptions disappeared. Attempts to isolate solid from this mixture or from reactions (incomplete by ir) run in DCE or THF, using the methods cited above for **44**, were unsuccessful.

The stoichiometry titration was run as for **44**, allowing somewhat longer time (~ 15 min) after each portion of ligand was added for the ir spectrum to stabilize.

Reaction of mercury(II) chloride with 4-diethylamino-3-butyn-2-one. On addition of 200 mg (1.4 mmol) **32** to a solution of 530 mg (1.9 mmol) $HgCl_2$ in 4 ml THF, a transient white precipitate appeared; the solution then cleared to a light orange. The ir spectrum of this solution shows three very weak absorptions at 2245, 2214, and 2175 cm^{-1} and bands at 1656(s), 1628(s), 1606(vs), and 1556(s) cm^{-1}.

A solution prepared in the same way from 135 mg (0.49 mmol) $HgCl_2$ and 139 mg (1.00 mmol) ligand **32** in 3 ml THF showed a weak band at 2157 cm^{-1} (unbound **32**) and double bond stretching absorptions with nearly the same pattern as for the solution with excess $HgCl_2$: 1655(s), 1632(s), 1607(vs), 1552(s) cm^{-1}.

A white precipitate appeared when this solution was poured into ~ 25 ml ether.

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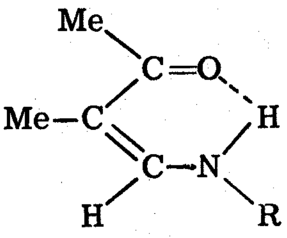
60. This point is made by implication in ref. 1b in which the authors note that in *cis, s-cis*  the two methyls "interact quite strongly."

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