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The Synthesis of Heterocycles from Vinylacetylenes or Diacetylenes and Nitrogen-containing Dinucleophiles

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Data on the reactivities of acetylenes substituted by conjugated electron donors or acceptors in heterocyclisation reactions with nitrogen-containing dinucleophiles are surveyed, the influence of the structure of the acetylenic component on the nature of the interaction is analysed, and the characteristics of the mode of intramolecular and intermolecular nucleophilic attack are discussed.
The bibliography includes 96 references.

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I. INTRODUCTION

Acetylenic compounds are being increasingly used in reactions leading to heterocycles. Processes such as the 1,3-dipolar cycloaddition, intramolecular cyclisation, cyclisation via a double attack on the acetylenic bond, and others have come to be widely used in the chemistry of acetylenes[1]. The vigorous development of this field can be explained by the extensive possibilities, discovered in the course of research, associated with the specific reactivity of the triple bond in nucleophilic addition reactions.

The synthesis of five- and six-membered heterocycles from 1,3-bifunctional compounds containing carbonyl groups is generally known. These data have been surveyed in a series of monographs[2-4] and also in a series of reviews (see, for example, Coispeau and Elguero[5]).

Numerous studies demonstrating that in the construction of heterocyclic compounds three carbon fragments can be formed by the reactions of conjugated alkenynes or alkadiynes with dinucleophiles have been published in recent years. The mode of the intermolecular nucleophilic attack on substituted acetylenes involving mononucleophiles has been discussed in a number of monographs[1,6] and reviews[7-9].

In the present review it is shown that the participation of conjugated systems in the construction of heterocycles is a general process, but the pathways leading to the formation of rings are different when unsaturated conjugated systems and 1,3-difunctional compounds containing carbonyl groups are used. In the first place the review deals with the acid-catalysed reactions of acetylenes, substituted by conjugated electron donors, with hydrazine, hydroxylamine, and guanidine derivatives, leading to the synthesis of pyrazoles, isoxazoles, and pyrimidines. Next, the available information about the reactions of the same acetylenes under the conditions of direct nucleophilic attack, leading to pyrimidines and pyridines, is surveyed. Finally, data are presented on the reactions of dinucleophiles with acetylenes substituted by electron acceptors—ethynyl residues.

II. CYCLISATION IN ACID MEDIA WITH PARTICIPATION OF CONJUGATED ACETYLENES

The reactions of dinucleophiles with acetylenes containing conjugated donors—1-heteroalk-1-ene-3-ynes (I)—in acid media via a mechanism different from that of the cyclisation of 1,3-dicarbonyl compounds are of greatest importance in the synthesis of heterocycles. This mechanism is based on the reactions of the protonated form of the acetylenic compound.

Compounds of type (I) can undergo hydrolysis and (or) hydration in an acid medium[10-12]:

$$\underset{(I)}{RXCH{=}CHC{\equiv}CH} \rightarrow \begin{cases} \rightarrow CHOCH_2C{\equiv}CH \\ \quad (II) \\ \rightarrow RXCH{=}CHCOMe \\ \quad (III) \end{cases} \rightarrow \underset{(IV)}{MeCOCH_2CHO}$$

Heterocyclic systems can therefore arise in principle as a result of the interaction of the nitrogen-containing base with both the protonated form of the initial compound and with its hydrolysis or hydration products.

1. Protonation of Acetylenes Substituted by Conjugated Electron Donors

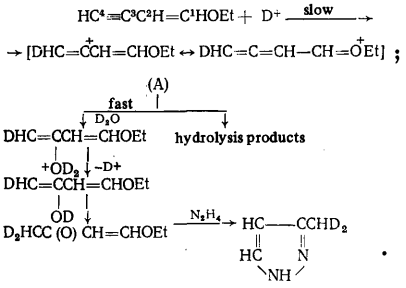
It has been shown[10,12] that the acid hydrolysis of 1-alkoxyalk-1-en-3-ynes leads to the formation of β-acetylenic aldehydes, but the authors do not present evidence for the structure of the hydrolysis products. The acid hydrolysis of the "usual" vinyl ethers[13-16] is faster by five orders of magnitude than the hydrolysis of 1-alkoxybut-1-en-3-ynes[17-19]. This fact is treated as evidence for a change in the reaction mechanism[17], total hydrolysis being preceded by the hydration of the triple bond and subsequent cleavage to acetoacetaldehyde. The mode of protonation of the conjugated system in hydrolytic reactions has been demonstrated by ^{1}H NMR [20,21] for substituted enyne ethers.

The study of the kinetics of the hydration of 1-alkoxybut-1-en-3-ynes has shown[22] that the rate of the reaction is determined by the protonation of the $C_{(4)}$ atom with formation of a conjugated carbonium ion (A), which is attacked by water molecules in the subsequent rapid stages. This is supported by the value of the isotope effect (k_{H_2O}/k_{D_2O} = 2.9); furthermore, the low entropy of activation for the hydration process (ΔS = 6.72 J mol^{-1} K^{-1} [18]) shows that in the transition state of the rate-determining stage of the process water is not firmly bound (Taft's concept[23,24]).

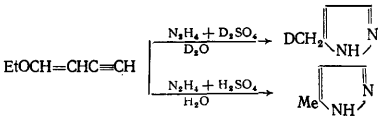
The common stage in the hydrolysis[20,21] and hydration[22] of the compounds RO–CH=CH–CH≡CR is apparently the protonation of the system at the $C_{(4)}$ atom and the formation of a mesomeric cation of type (A); the subsequent pathways in

the reaction of the cation are determined by the interaction with the electrophilic $C_{(1)}$ (hydrolysis) or $C_{(3)}$ (hydration) centre:

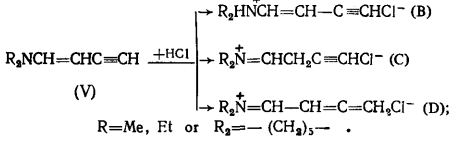
Scheme 1



When a nitrogen-containing base (hydrazine) was introduced into the reaction medium, the product of the direct interaction with the conjugated carbonium ion was isolated[22], which demonstrated the possibility of the direct cyclisation via the attack on the electrophilic centre $C_{(1)}$ or $C_{(3)}$ by a stronger nucleophile:



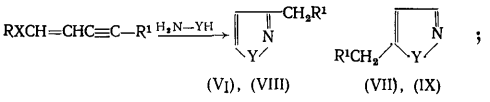
Alkynylenamines exhibit a higher reactivity in heterocyclisation reactions than the sulphur- and oxygen-containing analogues. The increased activity of the electrophilic centre at $C_{(1)}$ can be explained in this instance by the structure and properties of the protonated form produced under the cyclisation conditions[25]. Of the three possible types of salts, salt (B), which is rapidly converted via a protropic rearrangement into salt (D), is formed initially in the protonation of tertiary amines (V):



The allene structure of the immonium salts (D) has been confirmed in infrared and ultraviolet spectroscopic studies of the products of the mercuration of these amines[25]. Data[26,27] for the protonation and mercuration of enamines confirmed the immonium structure of the protonation products of amines of the vinylacetylene series. When the salt is attacked by a nucleophile, the $C_{(1)}$ reaction centre, activated by nitrogen, reacts preferentially.

2. The Reactions of the Protonated Forms of Acetylenes with Hydrazine, Hydroxylamine, and Guanidine Derivatives

The interaction of the conjugated carbonium ions examined above with bifunctional nucleophiles can take place with participation of the $C_{(1)}$ or $C_{(3)}$ reaction centre, i.e. with formation of heterocycles substituted in different ways; both possibilities are actually realised. The reactions of heteroenyne compounds with hydrazine, substituted hydrazines, and hydroxylamine, which permit inferences to be drawn concerning the reaction pathways of the conjugated carbonium ion, lead to the formation of two pyrazole isomers (VI) and (VII) or isoxazole isomers (VIII) and (IX):[28-33]



(VI), (VIII) (VII), (IX)

R^1=H, Me, Et, n-Bu, or t-Bu; Y=NR^2 (VI, VII); Y=O (VIII, IX).

The nature of the substituent X (for R^1 = H) exerts the most significant influence on the relative activities of the two reaction centres. If RX is an electron-donating substituent (an amino-,[29] an alkoxy-,[30] or an alkylthio-group[31]), for which the mesomeric effect predominates over the inductive effect at the instant of the reaction, then the reactivity is correlated with the positive mesomeric effect of the heterogroup and varies in the sequence $R_2N > RO > RS$.

Since in an aqueous acid medium the stage completing cyclisation is the reaction of the carbonium ion with the nucleophile[22], the structure of the final product is to a large extent determined by the activity of the $C_{(1)}$ and $C_{(3)}$ electrophilic centres in the conjugated carbonium ion. For X = NR, the electrophilic $C_{(1)}$ centre exerts the greatest influence and the main products are the isomers (VII) and (IX).[29] For X=O, there is competition between the electrophilic $C_{(1)}$ and $C_{(3)}$ centres, the role of the latter centre increasing on passing from oxygen to sulphur-containing derivatives in conformity with the decrease of the +*M* effect in this sequence[30].

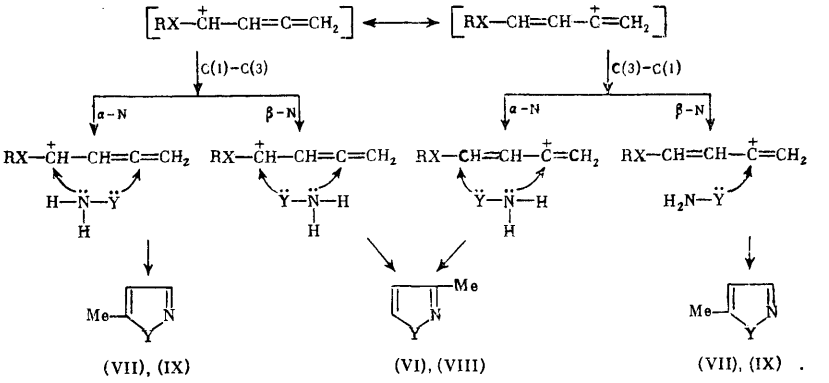
The influence of the nature of the substituents at the acetylenic linkage (R^1) is not manifested to quite such an extent. Substitution reduces the activity of the $C_{(3)}$ centre as a result of polarisation effects and steric factors; this increases the amount of 5-substituted pyrazoles or isoxazoles[33]. The influence of substitution at the acetylenic bond can be analysed from data for the synthesis of isoxazoles by the interaction of the homologues of 1-methoxybut-1-en-3-yne with hydroxylamine[30]. The amount of isomer (IX) increases in the homologous series.

On the other hand, the nitrogen-containing dinucleophiles $H_2N{=}YH$ (Y = O, NH, NA, or NMe) can react with the $C_{(1)}$ electrophilic centre of the carbonium ion via two alternative pathways: (1) attack on the α-nitrogen atom [the formation of isomers (VII) and (IX)]; (2) attack on the β-atom (oxygen or nitrogen) [the formation of isomers (VI) and (VIII); see Scheme 2].

For H_2NOH, the sharp difference between the nucleophilic properties of the two centres of the base (nitrogen and oxygen) improves the picture—the primary amino-group reacts with the $C_{(1)}$ centre of the carbonium ion [$C_{(1)}$–$C_{(3)}$ α-N-attack, isomer (IX)]. Such data have been obtained for X = NR; the reaction of 1-dialkylaminoalk-1-en-3-ynes with hydroxylamine leads to the specific synthesis of 5-alkylisoxazoles[29]. In view of the foregoing, one must emphasise the comparative value of the method, because the use of dicarbonyl compounds as starting materials results in a mixture of 3- and 5-alkylisoxazoles[3].

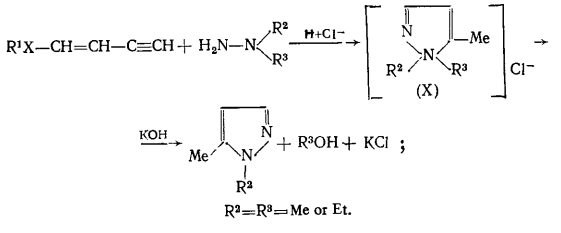
A comparative estimate has been made of the reactivities of the two-centres (α- and β-) of asymmetric hydrazines[33]. In monoalkylhydrazines the substituted nitrogen atom is more nucleophilic and it is therefore logical to postulate the possibility of β-N-attack on the electrophilic $C_{(1)}$ centre. However, in the reaction of 1-dialkylaminobut-1-en-3-ynes with methylhydrazine only between 5 and 15% of isomer (VI) is formed as a result of an attack of this type ($C_{(1)}$–$C_{(3)}$),

Scheme 2



β-N).[29] In $H_2N-NHAr$ the nucleophilic activity of α-N is higher than that of β-N, so that attack on the electrophilic $C_{(1)}$ and $C_{(3)}$ centres by the α-nitrogen atom of phenylhydrazine predominates for X = NR, O, or S.

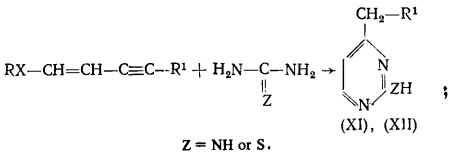
Asymmetric dialkylhydrazines $H_2NNR^2R^3$ reacted anomalously with enyne amines, ethers, and sulphides (X = NR, O, or S)[33]—the $C_{(1)}$ centre was attacked exclusively by the less nucleophilic α-nitrogen atom. The cause of the anomaly is apparently steric hindrance. Cyclisation led to the formation of quaternary pyrazolinium salts (X), which underwent the Hofmann degradation under the influence of concentrated alkali with formation of 1,5-dialkylpyrazoles (20%) and also the aminonitrile rearrangement[34]:



$R^2=R^3=$Me or Et.

With the exception of asymmetric dialkylhalides, the nitrogen-containing bases examined exhibit the α-effect in nucleophilic addition reactions involving the carbonyl group and in nucleophilic substitution reactions[36].

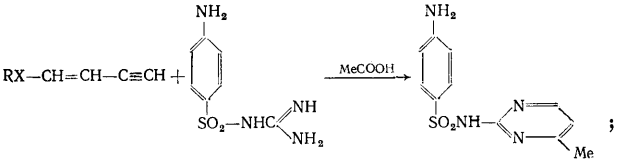
The reaction of a carbonium ion with nucleophiles such as guanidine and its derivatives leads to the formation of pyrimidine bases. Alk-1-en-3-ynyl ethers and sulphides react with guanidine or thiourea in an acid medium to give 4-alkyl-2-aminopyrimidines or 4-alkyl-2-mercaptopyrimidines [compounds (XI) and (XII)]:[37-39]



Z = NH or S.

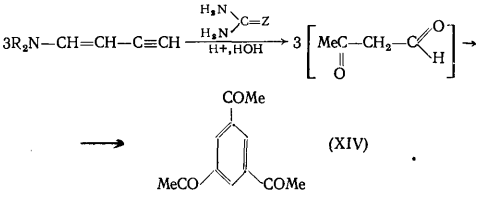
2-Amino-4-methylpyrimidine is used in the synthesis of pharmaceutical preparations[41]. Pyrimidinethiols accelerate the vulcanisation of rubbers[40].

The synthesis of sulfamerazine [2-(*p*-aminobenzenesulphonamido)-4-methylpyrimidine (XIII)], a long-action sulphonamide preparation, by the reaction of 1-heterobut-1-en-3-yne with 2-*p*-aminobenzenesulphonylguanidine is also of practical interest[42]:



RX = Et_2N, EtS, or EtO.

When 1-dialkylaminobut-1-en-3-yne is condensed with guanidine or thiourea in an acid medium, pyrimidine derivatives are not formed[37]. Only triacetylbenzene (XIV)—the product of the trimerisation of acetoacetaldehyde—was isolated from the reaction mixture. Thus, the reactions of a carbonium ion with water (hydrolysis, hydration, and trimerisation) are faster than the interaction with the nitrogen-containing base, which leads to pyrimidines:

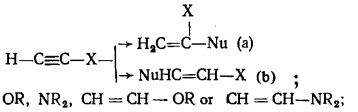


The results show that, among the three parameters (basicity, polarisability, and α-effect) characterising the reactivity of the nitrogen-containing base, the last factor apparently plays a significant role.

Evidently in an aqueous acid medium hydrolysis and hydration are not obligatory intermediate stages in the reaction with nitrogen-containing dinucleophiles. This view is based on the experiments, discussed above, using labelled atoms as well as data for the reactions of 1-dialkylaminobut-1-en-3-ynes with guanidine in an acid medium, which show that in the course of the reaction the hydrolysis and hydration products do not interact with nitrogen-containing dinucleophiles.

III. THE HETEROCYCLISATION OF ACETYLENES SUBSTITUTED BY CONJUGATED ELECTRON DONORS UNDER THE CONDITIONS OF DIRECT NUCLEOPHILIC ATTACK

The mode of intermolecular addition of nucleophiles to acetylenes of the type $H-C\equiv C-X$ is determined by the nature of the donor X:

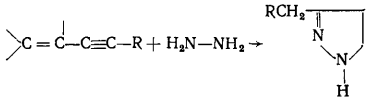


(a) X = OR, NR_2, CH = CH — OR or CH = CH—NR_2;
(b) X = SR or CH = CH — SR.

Thus, under the conditions of intermolecular attack, the nucleophile enters the α-position in alkynyl ethers (X = OR), enynyl ether (X = CH=CH–OR), and their nitrogen-containing analogues (X = NR_2 or CH=CH–NR_2) and the β-position in ethynyl sulphide (X = SR) or enynyl sulphide (X = CH=CH–SR).[45] This difference in the mode of addition is associated with the nature of the donor. The main factor responsible for the difference between the chemistry of sulphur, on the one hand, and that of oxygen and nitrogen, on the other, is the presence of *d* orbitals and the capacity for π–*d* interaction. These features are responsible for the attack on the β-carbon atom[46].

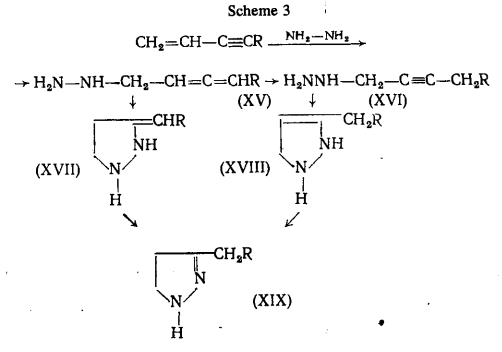
In cyclisation reactions the configuration of heterosubstituted enynes of all three types is the same ($C_{(1)}-C_{(3)}$ or $C_{(3)}-C_{(1)}$). The most varied heterocyclic compounds can be obtained from acetylene derivatives substituted by conjugated electron donors or nucleophiles capable of adding to a triple bond.

The only instance of the interaction of vinylacetylenic systems with hydrazine known in the literature refers to the synthesis of pyrazolines[47]:

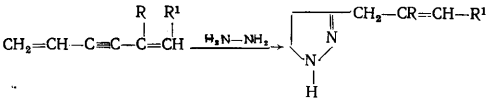


The authors[47] suggest that hydrazine adds in the 4,1-positions with subsequent cyclisation of the intermediate allene derivatives (XV) and the acetylene derivatives of hydrazines (XVI) to the unstable heterocycles (XVII) and (XVIII), which isomerise irreversibly to stable final 2-pyrazolines (XIX):[48]

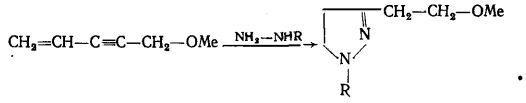
Scheme 3



In the reactions with mono- and di-substituted homologues of divinylacetylene hydrazine adds to the 4,6-positions with formation of 3-allylpyrazolines:

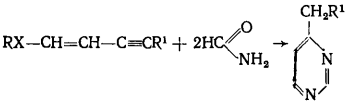


Hydrazine adds to the triple bond of isopropenylethynylmethanol[49]. Enynyl ethers with a non-conjugated alkoxy-group combine with monosubstituted hydrazines in the 1,3-positions[50]:

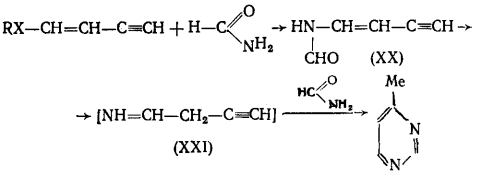


If the three-carbon fragment consists of a 1,3-conjugated enyne system, while the nitrogen-containing fragment is an amidine, thiourea, urea, guanidine, or formamide, the reaction products are pyrimidine derivatives.

4-Alkylpyrimidines have been obtained by the reaction of 1-heteroalk-1-en-3-ynes with formamide:[39, 51]

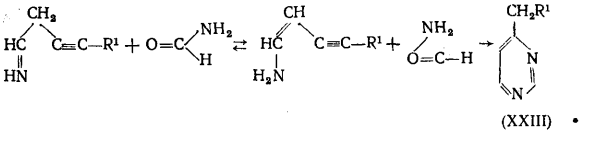


The reaction of alk-1-en-3-ynes probably proceeds via the nucleophilic substitution of the hetero-group by the amino-group of formamide with formation of the formamido-compound (XX) and the imine (XXI):



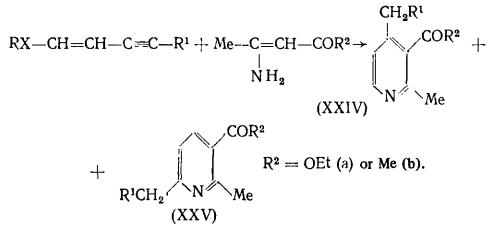
Such transamination has been proved by the isolation of dialkylformamides in the reaction with 1-dialkylaminobut-1-en-3-ynes[39]. The substitution of the stronger nucleophile (the dialkylamino-group) by the amino-group of formamide is possible according to the Law of Mass Action—when a tenfold excess of formamide is introduced into the reaction.

The formamido-compound (XX) is decarbonylated to the imine (XXI). Although the latter could not be detected, examples of stable compounds (XXII) of this kind have been described in the literature; they have been obtained by the reaction of formamide with benzoylacetone and were subsequently converted into pyrimidines at 220 °C.[52] The iminoketone is a proven intermediate in Bredereck's pyrimidine syntheses[53–56]. The imine (XXII) reacts with a second formamide molecule to form the pyrimidine ring (XXIII):



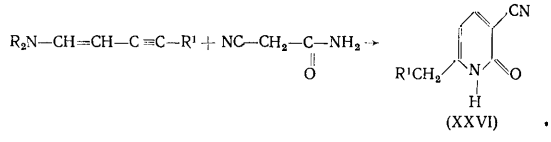
In the synthesis of pyridine systems, 1-dialkylamino(1-alkoxy)alk-1-en-3-ynes can be used as the three-carbon donors[57,58]. The two-carbon fragment can be supplied by enamines (for example, ethyl β-aminocrotonate), acetylacetone imine[57,58], and cyanoacetamide[29]. The main reaction

products are respectively ethyl 4-alkyl-2-methylnicotinate (XXIVa) and 3-acetyl-4-alkyl-2-methylpyrimidines (XXIVb) (90%, gas–liquid chromatographic method):



The proportions of the isomeric esters of 2,4-dimethyl- and 2,6-dimethylnicotinic acids (XXIVa) and (XXVa) have been determined chromatographically and by ^{1}H NMR, the two methods yielding satisfactorily concordant results[58].

Alk-1-en-3-ynylamines[29] condense with cyanoacetamide to form 6-alkyl-3-cyano-2-pyridones (XXVI):



The reactions described above are of interest in the sense that the involvement of the medium is ruled out—the interaction occurs on direct mixing of the reactants.

The formation of two isomers in the reactions of alk-1-en-3-ynes and alka-1,3-dienes with enamines (ethyl β-aminocrotonate or acetylacetone imine) can be accounted for by the ability of the two electrophilic centres of the initial 1,3-bifunctional compound and the two nucleophilic centres of the imine to compete.

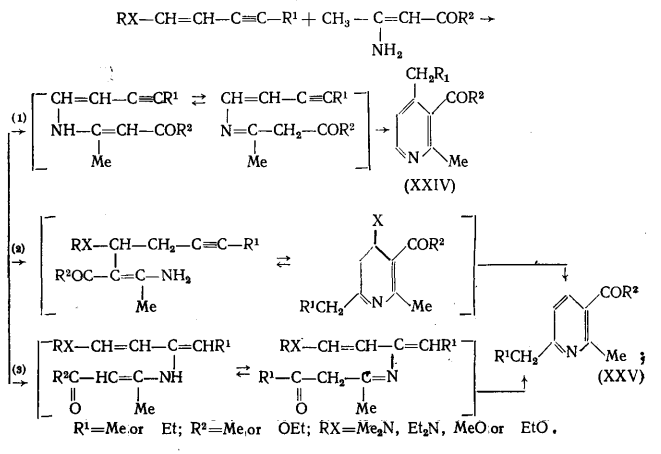
The above systems can interact with enamines in three ways.

1. Via the transamination of the hetero-group with participation of the $C_{(1)}$ reaction centre and intramolecular cyclisation involving the active methylene group and the C≡C triple bond: this results in the formation of the 2,4-isomer (XXIV).

2. By the Michael addition of the active methylene group to the C=C double bond and subsequent intramolecular cyclisation via NH attack [the formation of the 2,6-isomer (XXV)].

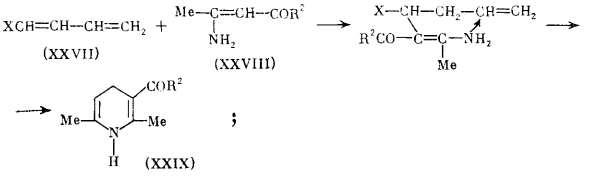
3. Via the nucleophilic attack by the primary amino-group on the $C_{(3)}$ reaction centre of the 1,3-enyne and cyclisation via the Michael addition involving the electrophilic $C_{(1)}$ centre of the conjugated system [the formation of the 2,6-isomer (XXV); see Scheme 4].

Scheme 4



Pathway (1) involves the initial addition of the primary amino-group to the electrophilic $C_{(1)}$ centre, which has a reduced electron density. This nature of the reaction presupposes the involvement of the free amino-group. Indeed, the stable *cis*-enamine structure of enaminoketones and enaminoethers unsubstituted at the nitrogen atom, stabilised by a hydrogen bond between the amino-nitrogen and the carbonyl oxygen, has been demonstrated in a number of studies[59–61].

Pathway (2) operates in the interaction of dienylamines with enaminoketones and enaminoethers with formation of isomers (XXIX) [58] (yield 10%):



Pathway (3) can apparently occur only for 1,3-substituted enynes, because there are data indicating the nucleophilic attack on the triple bond of hetero-substituted 1,3-enynes by primary amines[45]. The reactivities of the electrophilic $C_{(1)}$ and $C_{(3)}$ centres in alkoxyenynes in a neutral medium are comparable, which can account for the formation of up to 50% of the product resulting from the attack by the amino-group on the triple bond.

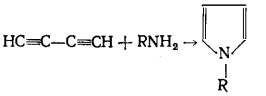
IV. THE REACTIONS OF ACETYLENES SUBSTITUTED BY CONJUGATED ELECTRON ACCEPTORS IN REACTIONS WITH MONO- AND DI-NUCLEOPHILES

Reactions involving the addition of primary and secondary amines of all types to triple bonds conjugated with activating groups of different kinds have been described in the literature[6,62].

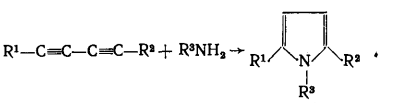
Thus the addition of primary amines to a diacetylene leads immediately to a 1 : 2 adduct[63], which undergoes the enamine—imine prototropic rearrangement[45,64]. Methyldiacetylene reacts with primary amines only at the unsubstituted acetylenic bond[65].

Secondary amines add to the 1,2-positions contrary to the Markovnikov rule[66–69]. Monoalkyldiacetylenes combine with secondary amines only at the terminal acetylenic bond[70]. Secondary amines add in the same manner to diacetylenic alcohols[71].

If the reaction of diacetylene with ammonia and primary amines is carried out in the presence of copper chloride, the products are pyrrole and its derivatives[72]:

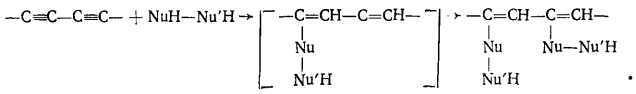


The reaction involving disubstituted symmetrical diacetylenes yielded 1,2,5-tri-substituted pyrroles[73,74]:



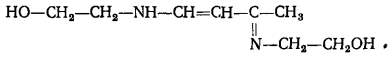
In this reaction the role of the catalyst consists in the formation of a non-polar π-complex with the triple bond, in which the electron density is uniformly distributed over both carbon atoms[75], which facilitates the closure of the pyrrole ring on interaction of the nucleophilic nitrogen with the fourth atom of the conjugated system.

The interaction of nitrogen-containing dinucleophiles with alka-1,3-diynes can proceed via two pathways—with formation of linear or cyclic structures. The mode of reactions of the first type resembles that of the reaction of diacetylene with mononucleophiles:

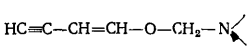


When there are two reaction centres of different strengths in the nucleophile, the centre with the maximum electron density reacts.

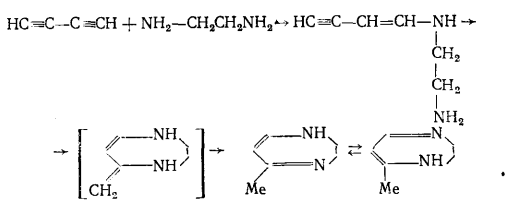
Thus, monoethanolamine adds to diacetylene as a primary amine, forming an adduct with a linear structure[76], which undergoes a prototropic transformation with fixation of the aminovinyl ketimine structure:



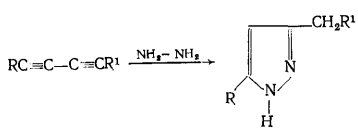
Aminoalcohols containing a disubstituted amino-group react with diacetylene to form adducts with a linear structure[77,78];



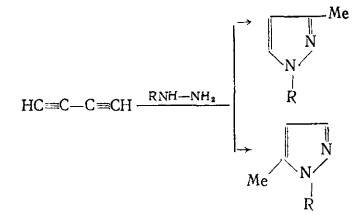
Aliphatic and aromatic diamines readily react with diacetylene, forming cyclic monoadducts. A seven-membered ring, corresponding to 1,3-addition, has been obtained from ethylenediamine[79]. Propylene-1,2-diamine adds to diacetylene in the same way[80].



Three groups of workers published comparatively recently [45,81,82] data concerning the possibility of synthesising pyrazole derivatives from diacetylene and its mono- and di-substituted homologues:

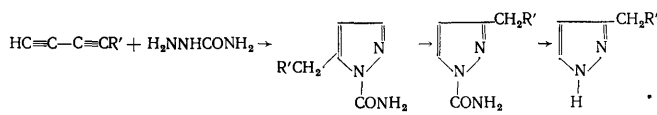


The remarks of different investigators concerning the mode of addition are inconsistent. Thus, when methyldiacetylene $HC^1{\equiv}C^2{-}C^3{\equiv}C^4{-}Me$ condenses with hydrazine hydrate[49], 3,5-dimethylpyrazole is formed together with 3(4)-ethylpyrazole, which confirms the possibility of a mixed attack on the conjugated diyne system in both the 1,3-positions and the 4,2-positions in proportions of 6 : 1. Furthermore, a study of the reaction of diacetylene with monosubstituted hydrazines[47] showed that in the absence of water the reaction leads to the formation of the 1,3-isomer, while in the presence of water the 1,5-disubstituted pyrazoles are obtained:[47,83]

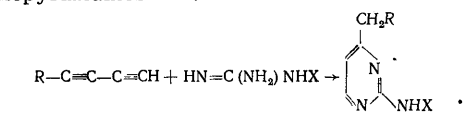


According to other data[84], the reaction of diacetylene with methylhydrazine in an alcoholic medium in the presence of sodium alkoxide leads to the formation of a mixture of isomeric 1,5- and 1,3-dimethylpyrazoles in proportions of 4 : 1.

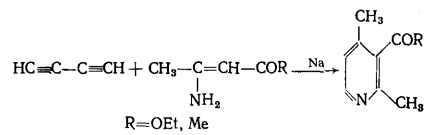
The amides of 5-alkylpyrazole-1-carboxylic acids, corresponding to the 1,3-mode of attack on the conjugated diyne system, have been obtained by the reaction of buta-1,3-diene and its asymmetric homologues (penta-1,3-diyne and hexa-1,3-diyne) with semicarbazide[85]; under the reaction conditions, the amides isomerise irreversibly to the amides of 3-alkylpyrazole-1-carboxylic acids according to literature data:



It has been established that diacetylene and its monosubstituted homologues react with guanidine or dicyanodiamide in the presence of equimolar amounts of sodium methoxide with formation of 4-alkyl-2-aminopyrimidines or 4-alkyl-2-cyanaminopyrimidines[86,87]:



The condensation of diacetylene with ethyl β-aminocrotonate or acetylacetone imine in the presence of equimolar amounts of metallic sodium results in the formation of ethyl 2,4-dimethylnicotinate or 3-acetyl-2,4-dimethylpyrimidine[88]:



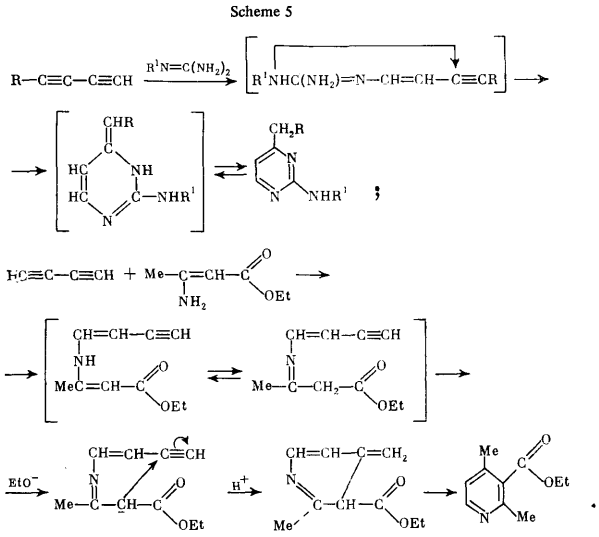
It is known that acetylenic residues have an electronegativity of the same order of magnitude as cyano-groups and a higher electronegativity than the carboxy- or carbonyl group[89]. In systems where the triple bond is conjugated with electron-accepting groups, which enhance the electron deficiency at the $C_{(4)}$ atom, the attack by the nucleophile is therefore directed to the terminal carbon atom of the triple bond.

In the $C{\equiv}C{-}C{=}O$ system, which has two electrophilic centres of different hardness, one-centre nucleophiles (alcohols, amines, CH-acids) add in the 4,3-positions. Two-centre nucleophiles such as hydrazine and semicarbazide (much stronger bases) add in the 1,2-positions, i.e. they attack the electrophilic carbon atom of the carbonyl group. Hydroxylamine (a weaker nucleophile than semicarbazide) reacts via both centres[90]. If the electron acceptor at the $C_{(1)}$ atom is "strengthened", the reaction of the system with hydrazine proceeds via the same mechanism as with amines. For example, the esters of ethyleneglyoxalic acid react with alkylhydrazines[90] via the triple bond (4,3-order of addition). The reaction of the nitriles of acids of the enyne series with hydrazine takes place in the $C_{(2)}{-}C_{(4)}$ positions. Hydrazine,

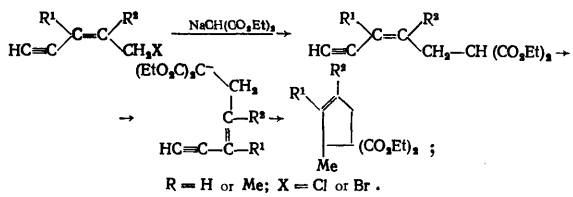
alkylhydrazines, and phenylhydrazine[91] add to these nitriles at the triple bond with subsequent cyclisation via the double bond and the formation of pyrazolines with a non-conjugated cyano-group in the side chain.

In the formation of six-membered rings, cyclisation takes place via the NH attack (pyrimidines) or CH attack (pyridines):

Scheme 5



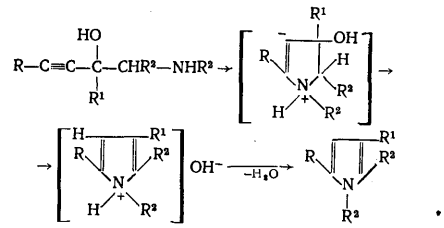
An example of the intramolecular CH attack on the acetylenic bond has been published[92]. The condensation of *cis*-1-chloropent-2-en-4-yne with sodiomalonic ester results in the formation of the diester of substituted 2-methyl-3-cyclopentene-1,1-dicarboxylic acid; the cyclisation takes place as the result of the interaction of the carbanion with the electrophilic centre of the triple bond:



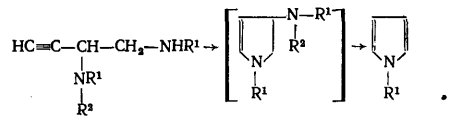
R = H or Me; X = Cl or Br.

Numerous examples of the intramolecular N–H addition to acetylenic bonds, leading to the formation of cyclic compounds, have been described in the literature. A thorough review[91] devoted to the intramolecular cyclisation of various types of acetylenic amines has been published recently. A significant factor in the formation of pyridine and pyrimidine derivatives is the tendency towards the formation of an energetically stable aromatic system. Thus the addition of primary amines to acetylene homologues[65] requires high temperatures and proceeds with much more difficulty than the reactions of the same homologues with guanidine and dicyanodiamide.

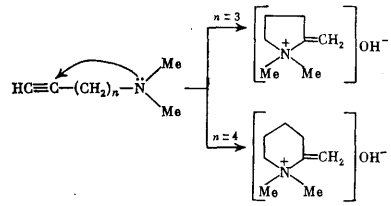
The nature of the reactions of acetylene derivatives containing the amino-group in a position non-conjugated with the multiple bond differs from that of the reactions just examined. α-Hydroxyethynyl alcohols react with primary amines to form β-aminoethynyl alcohols, which are converted into pyrroles on heating; the electron pair of the nitrogen atom then attacks the electrophilic centre of the triple bond and the resulting dipolar ion is stabilised by the simultaneous liberation of water and the migration of hydrogen[91]:



The intramolecular cyclisation of acetylenic diamines proceeds via the same mechanism but under more severe conditions, as a consequence of the reduced electrophilic properties of the triple bond[93]:

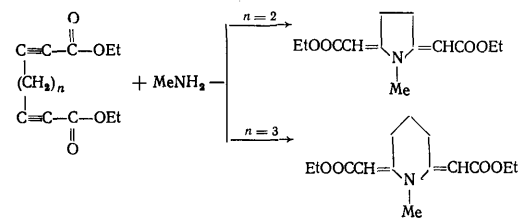


The tendency towards aromatisation apparently promotes the occurrence of these reactions, because tertiary acetylenic amines[94] cyclise at the second carbon atom. For $n = 2$, the reaction does not occur and for $n = 3$ or 4 quaternary ammonium bases derived from α-methylenepyrrolidine or α-methylenepiperidine are formed:

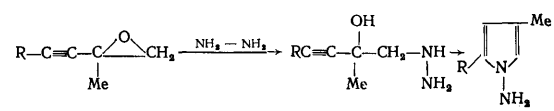


Here the nature of the attack on the acetylenic bond is different than in the examples quoted above[91,93] and corresponds to the polarisation of the acetylenic bond.

The double addition of primary amines to a non-conjugated diacetylenic system in the reaction of methylamine with esters of hexa-1,5-diyne-1,5-dicarboxylic or hepta-1,6-diyne-1,6-dicarboxylic acid is of interest[95]:



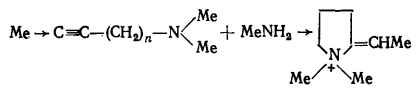
When hydrazine reacts with acetylenic epoxides, the resulting hydrazinoalcohols cyclise to five-membered heterocycles with elimination of the functional group and aromatisation of the system[96]:



In this case there is a possibility, in principle, of the formation of both five-membered and six-membered rings. However, only a five membered ring is obtained, because in the

transition state the reaction centres are in closer proximity on formation of five-membered rings.

The influence of the nature of substituents at the triple bond is pronounced in the absence of a conjugated bond system. Thus, in the series of tertiary acetylenic amines the replacement of hydrogen by an alkyl group makes the formation of five-membered rings difficult and six-membered rings are not formed at all:



The replacement of hydrogen by an alkyl group lowers the rate of the reaction but does not alter its general character.

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The data presented in this review show that electronic factors exert a decisive influence on the reactivity of the acetylenic bond in the reactions of the types considered. If the triple bond is conjugated with an electron donor, the attack by the nucleophile is directed to the α-carbon atom, while in conjugation to an electron acceptor the β-carbon atom is attacked.

The pathways leading to the formation of rings—the usual pathway (based on 1,3-dicarbonyl compounds) and the pathway described here (based on 1,3-conjugated systems)—have different mechanisms. In the first instance there is a two-stage process (for example, pyrazoles and pyrazolines are formed by hydrazones), while in the second instance both centres participate in the reaction, apparently synchronously, via a many-centre mechanism. The reactions described, based on unsaturated conjugated systems or bifunctional compounds, differ also in their results—isomers of different structures are formed; whereas the reactions with β-dicarbonyl compounds give rise to mixtures of isomers, in the second case there is a specific synthesis of only one of the two possible products.

The heterofunctional derivatives of vinylacetylene investigated do not enter into intermolecular reactions with many nucleophiles and do not combine with weak CH acids, while the cyclisation with participation of such substances takes place readily. Thus transformations which do not occur in intermolecular reactions do take place in cyclisation, the decisive factor being the tendency of the system towards aromatisation.

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