ASPECTS AND PROSPECTS OF THE CHEMISTRY OF ORGANIC HETEROCYCLES* (REVIEW). PART I

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The systematics of heterocycles, their place in organic chemistry, and their significance for theory and practice are discussed. Problems of the chemistry of heterocycles are discussed on the examples of systems with various types of conjugation and ring sizes. The focus is on the principles of synthesis of heterocycles, in particular, those based on acetylene, various C_3 fragments, carbon disulfide, and maleic anhydride. Individual sections of the survey are devoted to the role of heterocycles in biosynthesis, as well as certain problems common to the chemistry of heterocycles, biochemistry, and macromolecular chemistry.

1. INTRODUCTION

1.1. Heterocycles and Heteroatoms

Compounds containing not only carbon atoms but also heteroatoms (i.e., any atoms other than carbon and hydrogen), have had an extremely important effect on the development and even the establishment of organic chemistry: the "artifical formation of urea" from ammonium cyanate discovered in 1828 by F. Wohler [3], is based essentially only on the heterofunctional transformation of C_1-compound. Carbon disulfide and carbon tetrachloride were intermediate stages in the multistep synthesis of acetic acid according to H. Kolbe (1845, [4]), representing the first genuine synthesis of a carbon framework from elementary components.† Ultimately it was concluded that organic chemistry, which was first defined by C. Schorlemmer, can be considered as "the chemistry of hydrocarbons and the derivatives" (see [5, p. 9] and further [6, p. 122]), the chemistry of derivatives in which heteroatoms play the deciding role in giving variety to carbon compounds. Even in the case of a single carbon atom, bonded only to heterosubstituents, the possibility emerges for the construction of 75 main types of derivatives of carbonic acid with the aid of only four heteroatoms: oxygen (C—OH, C=O), nitrogen (C—NH, C=NH, C≡N), sulfur (C—SH, C=S), and chlorine (C—Cl).

*The present survey represents a reworking of material on the major pressing problems of the chemistry of heterocyclic compounds, previously published by the author [1, 2].

†It should be mentioned that in this case a whole series of synthetic methods that are still important were used (chlorolysis, pyrolysis, photolysis, electrolysis, "relay" synthesis of intermediate products, and an auxiliary synthetic role of heteroatoms). Only here was the independence of the chemistry of carbon compounds from *vis vitalis* substantiated and accorded universal recognition (see the notes in [6, p. 199; 7, p. 156; 8, p. 7]). F. Wohler's student, H. Kolbe, also emphasized "that it is impossible to construct a boundary between organic and inorganic." Each approach associated with the "chemistry of the organism" should have received its logical development in the biochemistry and molecular biology of our time: "Sciences as a whole, in the course of their development, have moved away from light and are being rejoined only by roundabout routes" (I. W. Goethe, in: Maximen und Reflexionen. Freiburg/Br. (1950), p. 115; originally quoted in the book Wilhelm Meisters Wanderjahre (1829), i.e., only a year after Wohler's discovery — a curious coincidence). The use of the term synthesis instead of the term artificial formation, a unique sort of metamorphosis, was long overdue; this concept was already coined in 1845 by H. Kolbe [4] and A. Hofmann [9]; however, in the modern sense this term was introduced and first comprehensively defined in 1860 by M. Berthelot [10] (see also [8, p. 8]).

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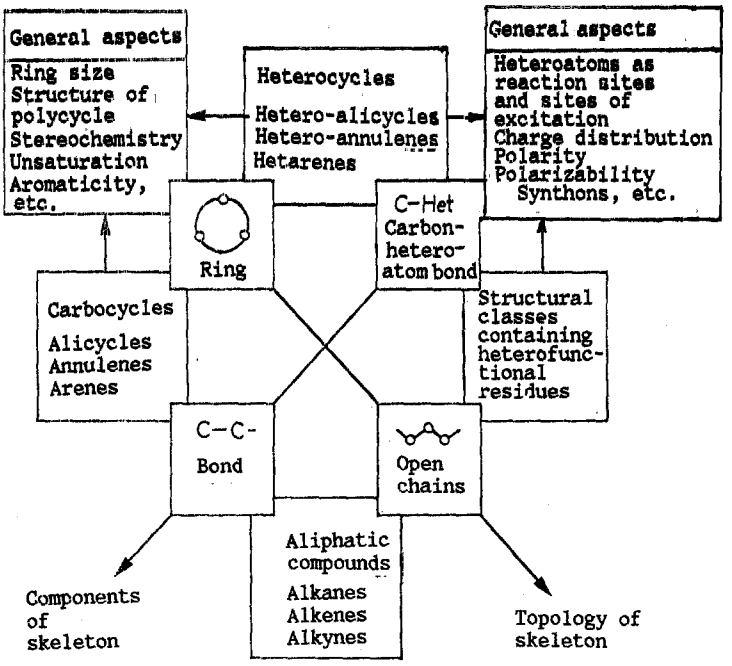

Fig. 1. Position of heterocycles in the system of organic chemistry.

Usually wide variety is exhibited in cases when heteroatoms, together with carbon atoms, form a circular framework of the molecule, i.e., an organic heterocyclic system (for general surveys see [11-18]; for the nomenclature of the heterocycles, see [16, 19]). In the broad meaning of the term, heterocycles include all compounds that have a ring-like molecular framework, consisting of at least two different types of atoms (a ring constructed from atoms of one type is a homocycle). In organic heterocycles, carbon is always present as an essential structural element (in the case of rings formed only by carbon atoms, it is a matter of carbocycles).

It is striking that at the early stages of development of organic chemistry, the autonomous classification of heterocycles caused obvious difficulties (cf. [5, 6, 11, 20, 21]). The classic definition of the "chemistry of hydrocarbons and their derivatives" essentially relegated heterocycles to a secondary role.* Heterocycles can be defined as products of "cyclizing H-substitution" of acyclic hydrocarbons, and thus can be considered as functional derivatives. For this reason the heuristic principle of H-substitution is rationally supplemented by a formal approach to the replacement of elements of the framework (see Sections 1.2 and 1.4).

The combination of carbon and heteroatoms into a cyclic molecule causes the appearance of a number of peculiarities. Compounds of this kind reflect the features of carbocyclic and functional structural classes to the same degree, and both these divisions, in turn, open up a broad spectrum of potentialities of organic chemistry, in which hetrocycles thus occupy a central position (see Fig. 1). The possible variety of structures already known for carbon ring systems, obtained by variation of the size of the ring, the formation of polycyclic systems, and the nature of the bonds at the elements of the ring, is supplemented by possibilities of variation of the nature, number, and position of the heteroatoms in the cyclic system. The heteroatoms are most often nitrogen, oxygen, and sulfur atoms; however, many other elements are also used (for example, phosphorus [22, 23], arsenic [24, 25], and tin [26]), interest in which in the chemistry of heterocycles is constantly increasing. By 1963, 15,000 heterocyclic systems had already been recorded [16, 27], and their number continues to increase.

*Since C. Schorlemmer ([6, p. 173]; cf. [7, p. 32]) characterized benzene as "marsh gases of the aromatic group, and since all other compounds are produced from it by replacement of hydrogen by elemental radicals," the definition of thiophene, pyrrole, pyridine, etc. as "marsh gases of heterocyclic groups" necessarily developed.

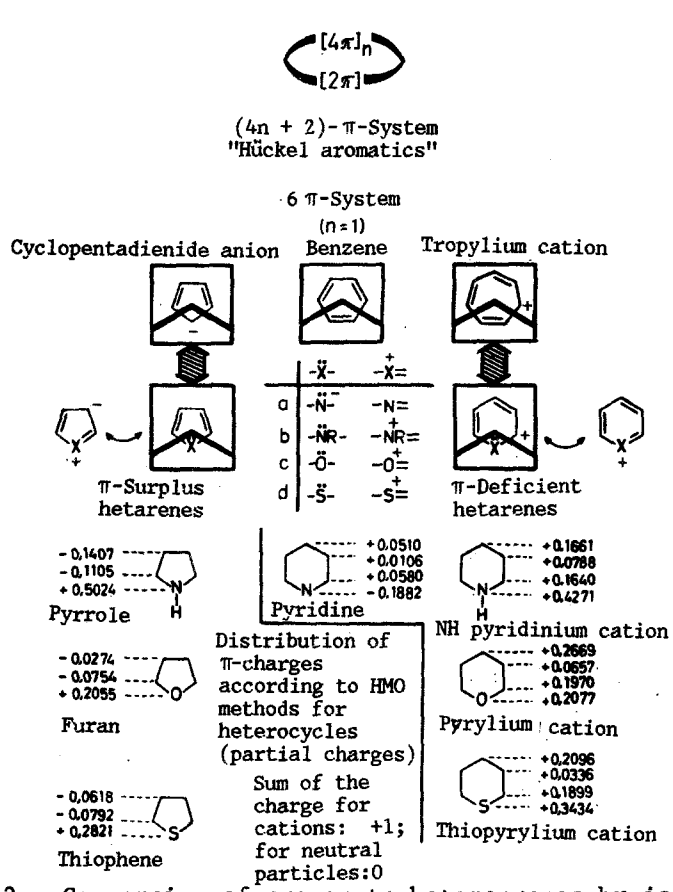

Fig. 2. Conversion of arenes to heteroarenes by isoelectronic substitution in the ring. Calculations of the densities of the π-charge cited according to the Hückel method of molecular orbitals (HMO) were performed by Schedler (Halle), using heteroparameters h_X, representing the theoretically substantiated coulombic integrals (see [29]) and the resonance integrals (the binding integral), corresponding to the values usually used (Streitwieser, Fabian, Zagradnii). For calculations *ab initio* for heterocycles, see [30, 31].

Heteroatoms perform a number of important functions in the organic molecule: a) they are structural elements of the σ-skeleton; b) they are included in the π-electron system (for example, in aromatic heterocycles); c) they represent a reaction site (reactions at the heteroatom: coordination, basicity, hydrogen bonds, etc.); d) they serve as a center of perturbations in the distribution of charges and the polarizibility of bonds (they affect the reactivity of their neighboring atoms). In the organic molecule the functions of the heteroatom are also expressed in various donor and acceptor effects, as well as in polarization of the system. Heteroatoms contained in functional groups play an important role in the course of synthetically useful reactions.

Thus, heterocycles can be perceived as unique electron-distorted copies of carbocycles or as cyclic variants or functional compounds. From this follows a whole of peculiarities, two of which should be taken up first: the role of the heteroatom in the cyclic system of conjugation and the significance of carbon-heteroatom bonds in the heterocycles for organic synthesis.

1.2. Heterocycles and Cyclic Conjugation

The chemistry of heterocycles is represented for the most part by compounds in which conjugation appears, similar to the conjugation in carbocyclic aromatic compounds (arenes), i.e., hetarenes*: in them the heteroatoms perform the functions of an element of the system

*Depending on the degree of unsaturation, we can also use the classification "heterocycloalkenes" and "heterocycloalkanes"; however, the inclusion of the last two cases in the general classification of heterocyclic compounds becomes doubtful under specific circumstances (compare with the statements in Section 1.4).

of conjugation; formally they replace carbon atoms of the ring of the carbocyclic aromatic hydrocarbons, thereby preserving the π-electronic structure of the latter (iso-π-electronic substitution in the ring) [7, p. 52] (for information on bioisosterism, see [28]). The π-electronic structure of heterocyclic compounds determines both their main properties and the specific differences of the heterocyclic structures from their acyclic analogs. In this case the possibility emerges for systematizing the π-electronic systems according to the nature, number, and position of the heteroatoms in the molecule.

Figure 2 serves as an illustration of what has been stated: first of all, let us recall E. Hückel's fundamental rule, 4n + 2 [32-34], which defines the closed π-electron group as a prerequisite for "aromatic" properties of a monocyclic conjugated system, or annulene (for information with regard to "aromaticity," see [7, p. 31; 27, p. 50; 35-40]; for a definition of "aromaticity constants," see [41, 42]; for the criteria of aromaticity for heterocycles, see [43, 44]). Since A. Kekulé proposed the formula for benzene (1865) [45, 46] (cf. also [47-49]), the problem of aromaticity still remains at the center of theoretical and experimental investigations to this day, and it is suggested as a heuristic principle in the consideration of significant discoveries and developments.*

In the establishment of the formula of benzene, the premises of bonding of the carbon chain into a ring, i.e., cyclic topology of the molecule (compare with [48, 49], were also expressed for the first time. E. Bamberger's hypothesis of six potential valences prompted a consideration of "aromatic" carbocycles and heterocycles from a single standpoint [53-55].† It was followed in 1925 by R. Robinson's concept of the aromatic skeleton [56] (see also [7, p. 34]). At the beginning of the thirties, quantum chemical studies of E. Hückel appeared [32-34].

The best known are the 6 π-electronic systems (n = 1), typical representatives of which are benzene, the cyclopentadienide anion, and the tropylium cation. Derivatives of these systems are the parent compounds of the classic series of five- and six-membered hetarenes, in which the heteroatoms (nitrogen, oxygen, or sulfur) play the role of a "π-equivalent" of the carbanion, ethene, or methine fragment of the ring. Depending on the ratio between the number of elements in the ring and the number of π-electrons, the density of π-charges on the carbon atom in a heterocyclic in comparison with benzene may be higher or lower; moreover, the degree of these differences is determined by the nature of the heteroatom. In principle, five-membered heterocycles with one heteroatom are characterized by an increase ("π-excess hetarenes") in the π-electron density on the carbon atom, while six-membered heterocycles are characterized by a decrease in it (" -deficient hetarenes," see [11] and originally [14]). The indicated pattern is manifested in the reactivity of these compounds; the former interacts primarily with electrophiles, and the latter with nucleophiles. Although their reactivity is sometimes comparable with the reactivity of enamines, enol esters, enones, or imines [57], such comparison permits a clear establishment of the degree of influence of the "aromatic" π-electron skeleton as a factor stabilizing the heterocyclic system and a determination of the degree to which "similarity to benzene" is reflected in the properties of the functional group.

1.3. Heterocycles in Organic Synthesis

The synthesis of heterocycles is promoted by various factors, including: the appearance of a stable (for example, aromatic) π-system as a driving force, kinetic preference caused by entropic effects, the formation, as a rule, of a profitable carbon–heteroatom bond, or more rarely, closing of a ring activated by a heteroatom at the stage of formation of C–C bond, and often the possible selection from several intermediate steps and pathways of synthesis. However, many syntheses lead to the formation of substituted or annelated compounds (for example, benzocondensed), whereas the unsubstituted first members of the series are frequently most readily available. Sometimes such systems can be produced by removal of a substituent. In this respect the heterocycles differ from a number of benzoid carbon rings in which the first members are produced commercially, often on a large scale, and their varied conversions can occur by H-substitution.

*We should also mention the fundamental relationships between aromaticity and pericyclic reactions (the Evans principle) [50-52].

†In [55] a characterization of the term "aromatic compound," extending it for the first time beyond the framework of the benzene formula, was given.

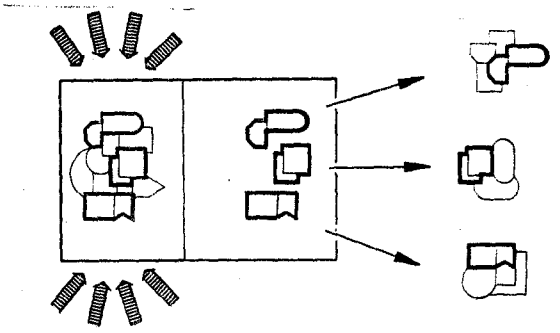

Fig. 3. Symbols of the transformation of structural elements and the essence of the changes in the course of organic synthesis (structural elements transferred in the course of synthesis are outlined.

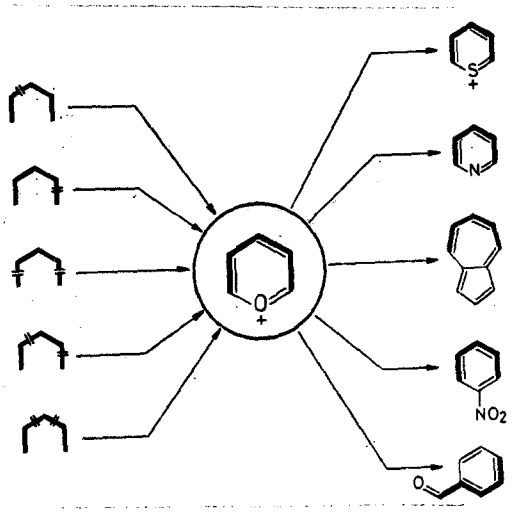

Fig. 4. Key role of the pyrylium cation in organic synthesis and its use in certain transformations of the ring.

A whole series of reactions characteristic of the chemistry of heterocycles, such as reactions of cyclization, ring breaking (destructive reactions), transformation of the ring [58-60], as well as reactions of substitution and addition, on a whole, constitute a very rich pool of possibilities that could be developed synthetically [61, 62]* ("latent functionality" of heterocyclic structures [63-65]). This synthetic potential of heterocycles is taking on increasing significance, since during the modern renaissance of synthetic organic chemistry [66-69], the arsenal of new methods and strategies has been developing rapidly.† Syntheses in which heterocycles participate thereby represent an extremely important supplement to the synthesis of heterocycles (a unique "turntable" for various directions of organic synthesis, "relay" synthesis; for a discussion of this concept, see [71-74]).

*According to [61] (in the preface), the first attempt to include the chemistry of heterocycles in the extensive field of synthetic organic chemistry was made by Morton [62]: "heterocyclic compounds frequently are extremely convenient as a source of nonheterocyclic substances."

†In [67] it is stated: "Synthesis as applied dynamics pertains to the most differentiated and creative fields of chemistry..." In the preface to the monograph [70], we can find a noteworthy statement: "Many brilliant books have been written about the organic synthesis of complex molecules. They accomplish the translation from the language of synthesis to the language of organic chemistry. I have attempted... to teach people to speak in the language of synthons and to dissect structures into fragments." However, this means that "organic chemistry" and "synthesis" speak in different languages (see also section 3).

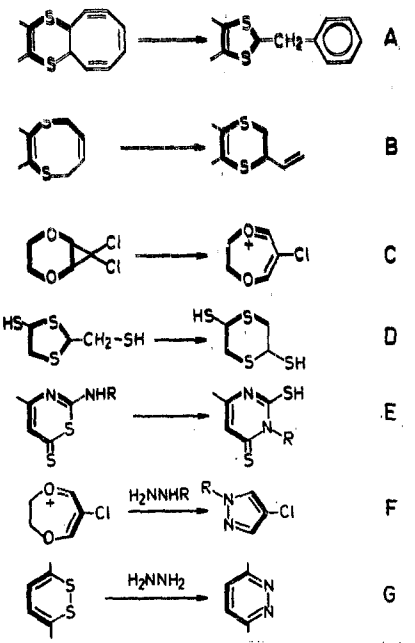

Fig. 5. Some transformations of heterocyclic systems.

Modern approaches to the methodology and logic of synthesis [8, 57, 63-66, 70, 75-84], to the planning of synthesis, based on a concept of synthons* and using computers, have also been closely linked with the development of the chemistry of heterocycles [85-92].† The use of computers is a necessity, taking into consideration the increasing rates at which experimental investigations are advancing and the theoretical prediction of the course of the reactions that competes with them. The selective utilization of reactivity due primarily to heterolytic reactions, induced by a carbon–heteroatom bond, remains at the center of attention [90-95]. In [76] a differential list of various types of selectivity was cited.

Using a series of drawings we can attempt to explain the situation: Fig. 3 illustrates the "transformation of structural elements" — a characteristic feature of organic synthesis, from which a comparison with the "overload area," the "storehouse," or the "reservoir" of synthetic elements of the structure, which is also symbolic of the role of heterocycles in

*In the original formulation of [75], synthons are "structural units that are associated with possible synthetic operations." According to [70], the synthon represents a "generalized fragment: usually an ion, formed in the cleavage of the target structure (sometimes the concept of the synthon is used to denote a synthetic equivalent, i.e., a reagent performing a function of such a synthon, which itself frequently cannot be used on account of other insufficient stability)." Moreover, the term synthons is used for a "partial structures participating in reactions," while the corresponding schemes of skeletal conversions are called "equations of synthons" [89]. Often the concepts of "synthon" and "reagent" are erroneously identified. We are using the term synthon to denote a fragment of a molecule or molecular framework isolated by cleavage of the target molecule, i.e., retrosynthetically (on the basis of "reverse strategy"). This fragment permits a required conversion of a molecular structure, based for the most part on the formation of a C–C bond (i.e., on the direct strategy), to be carried out (the synthon as the "framework of the reagent," the reagent as the "carrier of the synthon") in a suitable functional formulation by, for example, electrophilic, nucleophilic, radical, oxidative, or reductive reactions or rearrangements. See also the discussion of the concept of the synthon within the framework of graph theory in [85].

†For a 20-step synthesis with five different possibilities at each intermediate stage, it is possible to determine the field of activity (the "tree of synthesis") as $5^{20} = 9{,}5 \cdot 10^{13}$ pathways of the synthesis of the end product [90]. This fact graphically demonstrates the mastery of human intellect in the planning of the strategy of chemical synthesis, since multistep syntheses of this kind can be accomplished without a full logical analysis, which requires titanic labor (here we recall the even significantly more grandiose 60-step synthesis of cobyric acid, the basis of vitamin B_{12} [66]).

organic synthesis, quite obviously follows (compare with the introduction to [61]). Further, this metaphor can lead to the conclusion that pathways of synthesis that lead to the formation of a definite product and arise from it are interrelated and often determine the synthetic value only jointly (for a determination of the significance of the intermediate product, see [96, 97]).

An excellent example from the chemistry of heterocycles is provided by pyrylium salts [98-106]* (Fig. 4): they can readily be obtained from various synthetic elements containing components from C_1 to C_5 ("formation of an aromatic system") and then in reactions with nucleophilic agents, once again readily converted to daughter products (high acceptor reactivity); moreover, in most cases a carbon fragment from C_1 to C_5 is transferred (see also [58-61]). The conversions cited here represent transformation of the ring. Reactions of this kind proceed primarily with the breaking of one bond and the formation of a new bond according to the system of carbon—heteroatom bonds.

Some typical examples of the transformation of rings based on the studies of the author are cited in Fig. 5 (here, as in all subsequent cases, the notations of the compounds, pathways of synthesis, etc. are preceded by the number of the corresponding figure, separated by a dash, for example, 5-D denotes reaction D in Fig. 5). Reactions 5-A to 5-D characterize a change in the framework of the molecule while the constituent atoms are preserved; reaction 5-E corresponds to a Dimroth rearrangement (for the classification of such a reagent, see [107]); in reaction 5-F the initial heterocycle is used as a "latent" chloromalonodialdehyde, while in reaction 5-G it is used as a "latent" 1,4-butenedione (reactions 5-A — [108, 109]; 5-B — [109, 110]; 5-C — [111]; 5-D — [112]; 5-E [113] see also section 2.3.3; 5-F — [114], see also section 2.1.1).

1.4. Heterocycles in Theory and Practice

Heterocycles have many important reasons of application; let us mention only dyes, blood preparations, agents for agrochemistry, monomers for polymerization, anitioxidants, and accelerators of vulcanization. In view of the constantly expanding requirement for the major and intermediate commercial products, the possibilities of rational technical production and use of heterocyclic compounds are also increasing. Evidently decisive progress in organic chemistry and its commercial application occurs on account of the development of new methods and new strategies of synthesis, on account of "highly enriched chemistry," on account of a better knowledge of the relationships between structure and properties (cf. [67, 69]), and in connection with this, the possibilities of the chemistry of heterocycles make a significant contribution.

The latitude of the variation of structures, possibilities of synthetic approaches, as well as the flexibility of the reactivity, ensure a leading position of heterocyclic compounds in biological processes; the existence of life is associated with heterocyclic structures, which is already confirmed by the biological function of cyclic bases in nucleic acids alone (see Section 2.8). We might also cite numerous other examples (the pigments of blood and leaves, vitamins, various amino acids, alkaloids, etc.). And finally, cellulose and starch, while belonging to the series of carbohydrates, still can easily be considered as high-molecular-weight heterocycles.

It is quite understandable that the chemistry of heterocycles for a long time seemed clouded by unrelated facts, more or less isolated from the rest of organic chemistry (see also Section 1.1). A generalizing treatment of this complex field was first developed with the appearance of substantiated theoretical concepts of structure and reactivity, with the growth of general experience in organic chemistry. Nowadays these compounds are increasingly widely used as testing grounds for quantum chemistry [115-119], for the investigation of the structure and mechanisms of reactions [120], for a constant and effective interaction

*In principle, pyrylium salts can be considered as a third member of the series of vinylene homolog carbonyl synthons, arising from halides of carboxcyclic acids through acylvinyl halides (see section 2.4), in accordance with the reactivity of a^1, a^3, and a^5 [100-103] (for the terminology of reactivity, see [76]).

Fig. 6. Heterocyclic 6-, 8- and 10π-electronic systems. I = 1,2-diheterete; II = 1,2-diheterin; III = 1,4-diheterin; IV = 1,4-diheterocine; V = cyclopenta[b]-(hetero)pyran; X = S, O, NR.

of theory and experiment,* which to a substantial degree promotes a narrowing of the diffuse area of trial and error in organic synthetic chemistry.†

And yet, many heterocyclic systems differing in the degree of their development and the level of information about them have become known: "representatives of extensive fields of chemistry, including classical types of hetarenes, are contrasted to the "exotic unique ones" (see Section 1.2). Suffice it to refer to the chemistry of thiazole, imidazole, and pyrimidine (for example, there are 4328 references in a monograph devoted to pyrimidine and published in 1970). How does the scientific profile of the chemistry of heterocycles look, where are its contours denoted? Two structural criteria denote its framework; moreover, each of them individually can be successfully assigned to other fields of organic chemistry as well. Such are the cyclic structure of the molecule and the presence of a heteroatom in the framework of the ring, together with carbon atoms. To the degree to which observance of both these prerequisites is compulsory, the concept of the chemistry of heterocycles also takes on significance (for example, hetarenes are an object of the chemistry of heterocycles in the narrower sense). The concept of the chemistry of heterocycles may be disputed if compounds are considered exclusively from the standpoint of one functional group (for example, cyclic amines in reactions of enamines, lactams in connection with acid amides, etc.). Once the boundaries have been exceeded, the evaluation may vary depending on the viewpoint. "The profile of the chemistry of heterocyclics" should be precisely outlined regardless of the subject: supplementary structural characteristics, criteria of reactivity, properties described in detail or individual analogies, etc. In this case the question of the transfer of the center of gravity to the nature of the heteroatom or carbon fragment ultimately is closely interlaced with the synthetic utilization of raw material resources (for example, syntheses of heterocycles on the basis of acetylene, carbon disulfide, or urea, "enrichment" syntheses using carbohydrates, alkaloids, or terpenes, etc.). From raw material resources to highly enriched products, from vitally essential biological functions to essentially theoretical questions — the richness of the content of these aspects outlines an almost all-encompassing area. We shall return to these questions again in Section 3.

2. SELECTED QUESTIONS

The sections that follow are based on studies conducted at the Scientific Division of Organic Chemistry (section of chemistry of Martin Luther University, Halle-Wittenberg) and presented to approximately the degree to which they reflect the problems formulated in the preceding sections (1.1-1.4) and contribute to the general picture. Information of this kind may also prove useful to students and young scientists for an understanding of such investigations and their prospects. Moreover, aspects of synthetic chemistry are taking the foreground, for understandable reasons. For our material on the classification of various studies, see [74]; for surveys on heterocycles, representing liquid crystals, see [125-128].

*"The interaction of theory and experiment is at the heart of any division of natural sciences. Theory and experiment supplement one another..., simultaneously promoting mutual progress, which could not be achieved otherwise" [118] (see also [121]).

†Impressions of the "trial and error" method in organic synthesis were rendered in [122] ("synthesis of prostaglandins: strategy and reality"). Compared with the optimistic thesis expressed in [123] ("Theoretical Chemistry and Organic Synthesis," p. 44): "...The joyful approbation of each step of the reaction scheme repels us from crystal-clear theoretical deductions back into the original premise. Comparing with the activity of architects constructing air locks, we can state that these splendid syntheses require connoisseurs of their work in organic chemistry." Considering the rates of development of organic chemistry on an international scale and on the basis of the situation in 1965, D. Cram expects that by the year 2000, "It will hardly seem strange that the tool of the future should be a giant mind... The researcher will have to master the possibility of selection..." (cited according to [124], p. 2]).

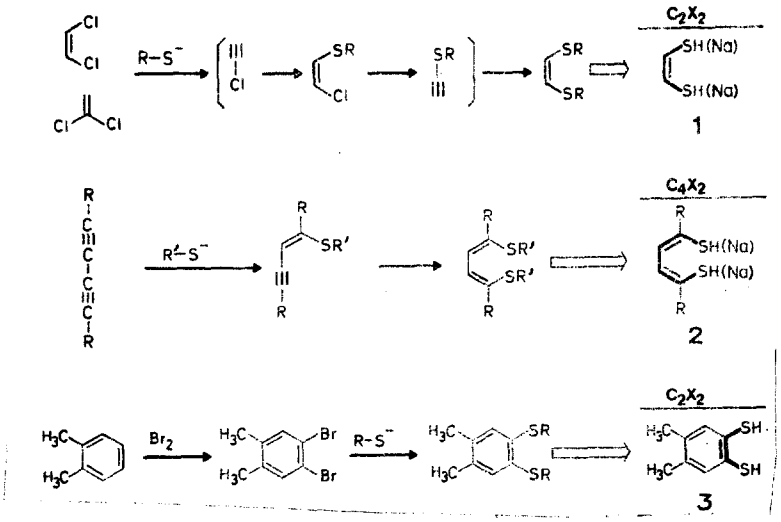

Fig. 7. Approaches to the synthesis of S-containing "blocks" — cis-1,2-dimercaptoethene (1), cis,cis-1,4-dimercaptobutadiene (2), and 4,5-dimercapto-o-xylene (3). The syntheses of compounds 1 and 2 are based on acetylene (see Section 2.2).

2.1. Conjugated Heterocyclic Systems: Possibilities and Boundaries of Conjugation in the Rings

The relationship between five- and six-membered hetarenes and carbocyclic 6π-systems, discussed in Section 1.2, prompts interest in the generalization of the heuristic principle of iso-π-electronic substitution in the ring.

This work pertains to a substantial degree to two theoretical questions: a) what is the situation in monocyclic conjugated systems corresponding to the region of 6π; b) whether replacement of one carbon—carbon double bond by two heteroatoms is theoretically possible in nonionic monocycles. In cationic (especially dipolar) 6π-systems, the replacement of a carbon—carbon double bond evidently is less problematical (for example, pyrazolium, imidazolium, thiazolium, 1,2- or 1,3-dithiolium cations on the one hand, and pyrazolones, imidazolones, thiazolones, 1,2- or 1,3-dithiolones, on the other hand). Formally a π-electronic equivalent to the tropylium cation and tropone exists here; also compare the situation in the case of sulfur-containing 6π-systems [129]. Studies of heterocyclic systems 6-I to 6-V have been oriented along this line (Fig. 6) [130]. With the incorporation of 2π-heteroatoms X into a system of cyclic conjugation, the number of π-electrons increases from 6 (6-I) to 8 (6-II and 6-III) and even to 10 (6-IV and 6-V).

As a rule, the main interest in evoked by the corresponding sulfur-containing representatives of heterocyclics, since among the five-membered hetarenes, the S-hetrocycle (thiophene) is also characterized by the greatest similarity to benzene. Another distinguishing feature of these vinylene homolog systems is the fact that they are constructed from structural fragments C_2X_2 and C_4X_2. Therefore, to obtain S-heterocycles, cis-1,2-dimercaptoethene (7-1) and cis,cis-1,4-dimercapto-1,3-butadiene (7-2) were necessary as new C_2X_2- and C_4X_2-structural elements in the cyclization reactions (see Fig. 7): cis-1,2-dimercaptoethene (7-1, or respectively, its disodium salt) can be produced by the reaction of cis-1,2-dichloroethene or vinylidene chloride* with benzyl mercaptide, followed by reductive cleavage of the cis-1,2-dibenzylthioethene [132, 133] (reaction 7-1; see also [112]). cis,cis-1,4-Dimercapto-1,3-butadienes (7-2, R = H, Alk, Ar) can also be produced by nucleophilic addition of benzylmercaptide to diacetylene (or, correspondingly, to disubstituted 1,3-butadiyne), followed by reductive cleavage of the cis,cis-1,4-dibenzylthio-1,3-butadienes formed [114, 134, 135] (or the production from 1,4-diketones, see [136]; also compare with [137]). In both syntheses we should note the regio- and stereospecificity of the nucleophilic substitution of the chlorine atom, which occurs without subsequent steps of elimination and addition. In the series of S-heterocycles, 4,5-dimercapto-o-xylene (7-3), produced from o-xylene without an intermediate stage of 4,5-dibromo-o-xylene [138-141], was used as the benzannelated and consequently configurationally fixed structural element of C_2X_2 [138-141].

*The use of vinylidene chloride as a 1,2-bis-receptor reagent was discussed in the dissertation [109], and its use in the synthesis of heterocycles in [31] (cf. Section 2.4).

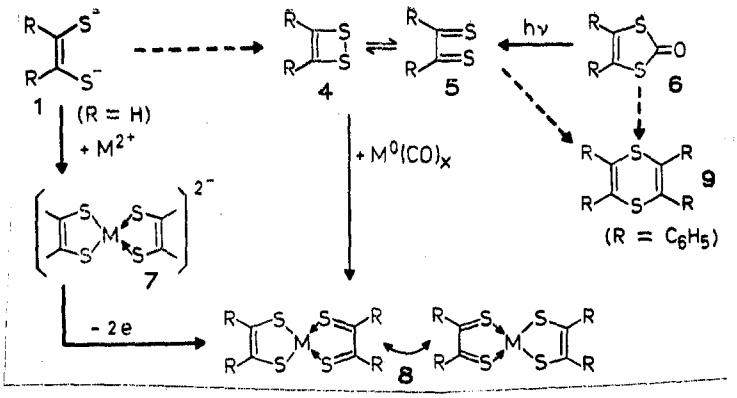

Fig. 8. Problems of the synthesis of 1,2-dithiete; approaches to chelate analogs of 1,3-dithiol.

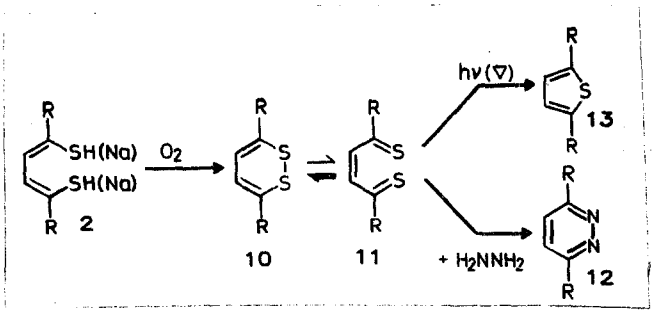

Fig. 9. Synthesis and reactions of 1,2-dithiynes.

2.1.1. 1,2-Diheterets of the Type of 6-I (Fig. 8)

1,2-Dithiet (8-4) (3,4-dithiacyclobutene) formally has 6π-electrons and thus should prove to be stabilized by "aromatic" delocalization of π-electrons. Moreover, the possibility of electrocyclic isomerism with the α-dithione structure 8-5 should also be reexamined [in the case of oxygen-containing compounds, α-dicarbonyl compounds (glyoxal, benzyle), of the predominance of the carbonyl form in which there is no doubt, are also possible]. The plan of synthesis of 1,2-dithiete (correspondingly, its valence isomer of the α-dithione type) by the oxidation of cis-1,2-dimercaptoethene (8-1) or from cis-1,2-diphenyl-1,2-dimercaptoethene, of course, remained unrealized [132, 133], although in the case of the xylene homolog cis,cis-1,4-dimercapto-1,3-butadiene 9-2 (see Fig. 9), analogous oxidation with the formation of a disulfide is possible, while dicyano-1,2-dithiete (8-4, R = CN) is clearly formed as an intermediate in the oxidation of dicyano-cis-dimercaptoethene (8-1, R = CN in the form of the corresponding disodium salt) [142]. Oxidation of cis-dimercaptoethene (8-1, R = H) in the form of a complex is also possible, since a reaction including a step of oxidation of the disodium salt of cis-dimercaptoethene by salts of transition metals to the chelates 8-8 is known, and the S-ligands present in these compounds should be considered as complexly stabilized α-dithiones [143-146] (for a survey, see [147]; cf. also [141]). Attempts have been undertaken to produce diphenyl-1,2-dithiete or, correspondingly, dithiobenzyl (8-4 and 8-5, R = C_6H_5) by photochemical cycloelimination of CO from 4,5-diphenyl-1,3-dithiolones-2 (8-6, R = C_6H_5); however, in this case tetraphenyl-1,4-dithiyne (8-9, R = C_6H_5) is formed in a high yield [148]. It is quite probable that the intermediate product in this process is dithiete, which then enters into subsequent reactions. Decarbonylation can be observed when the mass spectrometric method is used [148]. The possibility of fixing the dithiete corresponding to the α-dithione formed in the photolysis of 3-methylthio-5,6-tetramethylene-1,4,2-dithiazine in the form of a chelate with the aid of molybdenum hexacarbonyl was described in [149].

An exception is the photolysis of bis(p-dimethylaminophenyl)1,3-dithiolone-2 [8-6, R = p-$C_6H_4N(CH_3)_2$], in which the corresponding diaryl-1,2-dithiete [8-4, R = p-$C_6H_4N(CH_3)_2$] is formed and exists at equilibrium with the valence tautomer with α-dithione structure 8-5 [150] (for critical remarks, see [151, 152]). Up to this time, the only representative of this structural type can be considered to be bis(trifluoromethyl)-1,2-dithiete (8-4, R = CF_3),

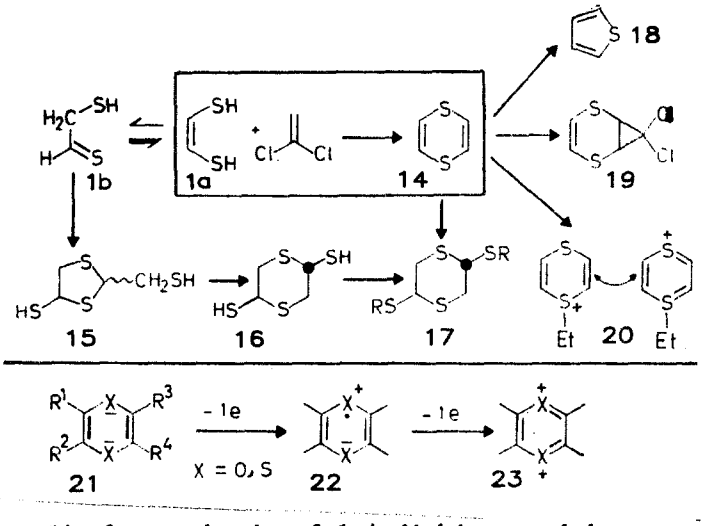

Fig. 10. Simple synthesis of 1,4-dithiyne and its reactions. Conversion of cis-1,2-dimercaptoethene.

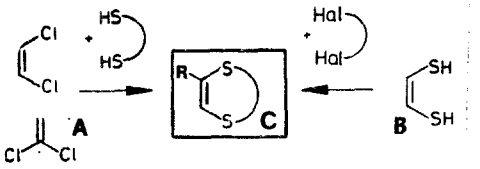

Fig. 11. Principle of "cyclovinylation" vor heterocycles including a 1,4-dithiobutene-2 fragment. Substituted cyclovinylating agents: $Cl_2CHCHCl_2$, $Br_2CHCHBr_2$; $PhCHClCHCl_2$, $PhC \equiv CCl$; R = H Cl, Br, Ph.

which, however, was produced in an entirely different way [153, 154]. As if follows from all the available data, the properties of the system of the 1,2-dithiete 8-4 are very greatly influenced by the effects of substituents; the question of interpretation of the results obtained from the standpoint of aromaticity still remains open.

2.1.2. 1,2-Diheterynes of the Type of 6-II (Fig. 9)

1,2-Dithiyne (9-10) (1,2-dithia-3,5-cyclohexadiene), like 1,2-dithiete, represents a cyclically conjugated disulfide (see the survey [155]). Formally the system possesses 8π-electrons, and, consequently, should be assigned to the "nonaromatic" 4n-theory (n = 2).

The synthetic approach to 1,2-dithiynes of the type of 9-10 was first implemented by the oxidation of cis,cis-1,4-dimercapto-1,3-butadienes 9-2 [135]. The extremely low stability of the first member of the series 9-10 (R = H) in alkaline medium, as well as the values of the chemical shifts in the ^1H NMR spectra, are evidence of its purely heteroolefinic character. On the other hand, it was revealed that 3,6-diarylated representatives of 9-10 (R = Ar) tend to be formed in the spontaneous oxidation of the corresponding dimercaptobutadienes 9-2 by atmospheric oxygen [114]. It is surprising that 1,2-dithiyne, which represents a conjugated system with only two C=C double bonds, proved to be colored (absorption maximum at 460 nm). We should consider the possibility of electrocyclic valence tautomerism with the product of opening of the ring of the type of 2-butene-1,4-dithione 9-11. However, all the experimental data support a cyclic dithiyne form 9-10 (nonetheless, directly opposite results were obtained for the analogous oxygen-containing compounds). Even reactions with hydrazine with the formation of pyridazines 9-12 and simultaneous liberation of H_2S, which is a possible indication of intermediate formation of an open valence tautomer 9-11, is found to proceed more complexly — through the heterocycle 9-10 (reduction back to dimercaptobutadiene 9-2, condensation with the formation of dihydropyridazine and subsequent oxidation).

From quantum chemical calculations considering all the valence electrons, it follows that the S–S bond has a negative order of the π-bond [114, 156], which is unusual in itself and may indicate a loosening of this bond or, in terms of the method of valence bonds, a resonance "without coupling" between the cyclic and open structures. 2,6-Disubstituted 1,2-dithiyne 9-10 readily split out sulfur, forming 2,5-disubstituted thiophenes 9-13. No doubt this is a clear example of destabilization of the conjugated heterocyclic system with 8π-electrons — a phenomenon which that was discussed recently [157]. And finally, 2,6-disubstituted 1,2-dithiynes 9-10 have been found in plants as representatives of biogenic thiophenes [158, 159].

2.1.3. 1,4-Diheterynes of the Type 6-III

1,4-Dithiones 10-14 (Fig. 10), like 1,2-dithiones, represent an 8π-electron system with two sulfur atoms and two C=C double bonds [160-162]. Certain C-substituted derivatives of this series were obtained from α-mercaptocarbonyl compounds; however, the synthesis of the first member of the series is difficult [163-165].

In this case, just as in general for heterocyclics including a 1,4-dithio-2-butene fragment, the most fruitful approach is heterocyclization of dimercaptans with vinylidene chloride or with cis-dichloroethene (the principle of cyclovinylation according to reaction II-A → 11-C in Fig. 11) and the interaction of cis-dimercaptoethene with dihalides (according to reactions 11-B → 11-C). The originator of the series — 1,4-dithione — can be obtained in a good yield from the disodium salt of cis-dimercaptoethene and vinylidene chloride corresponding to cis-dichloroethene [131, 166, 167].

The "cyclovinylation" of dimercaptans is an intramolecular variant of the method already used in the synthesis of cis-dithioethenes (Fig. 7) (see [110]). In addition to cis-dichloroethene and vinylidene chloride, all the C_2-halides that are capable of reacting according to an elimination–addition mechanism, depicted in Fig. 7 [167] (cf. also Fig. 11), can also be used as components of the cyclovinylation reaction. Such a course of the reaction was first described in the case of dimercaptans (for information on regioselectivity as a function of the nature of the nucleophilic agents, see Section 2.2).

1,4-Dithiyne acts as a heteroolefin: in catalysis by BF_3, mercaptans are smoothly added to the C=C double bond with the formation of trans-2,6-dialkyl(aryl)thio-1,4-dithianes 10-17 [112], identical with the products of S-alkylation of the dimer of cis-dimercaptoethene 10-16 (trans-2,6-dimercapto-1,4-dithiane), readily formed through steps 10-1b and 10-15. Subsequently halocarbenes began to be added (for example, forming 10-19 [11]). The elimination of sulfur with the formation of thiophene (10-18) requires substantially higher temperatures than in the case of 1,2-dithiones; in comparison with the latter, 1,4-dithiynes have shorter wave absorption maxima. In S-alkylation of 1,4-dithiynes, 1-alkyl-1,4-dithiynium salts 10-20 are obtained [168]; according to the data of the PMR spectra, they are rather strongly polarized, as shown in the formula of the limiting structure, depicted on the right; however, they do not possess cyclic delocalization of the 6π-electrons. As evidenced by the results of quantum chemical calculations and electrochemical oxidation, for 1,4-dithiynes and 1,4-dioxanes, easy stripping of a maximum of two electrons is possible. In accordance with this, tetraphenyl-1,4-dithiyne and tetraphenyl-1,4-dioxane (10-22, X = S, O; R^1–R^4 = C_6H_5) were oxidized by $SbCl_5$ to deeply colored crystalline salts 10-23, possessing a π-electron skeleton in the dication [169].

2.1.4. 1,4-Diheterocines of the Type 6-IV

In 1931 Hückel, on the basis of his 4n + 2 rule, already dared to announce: "For a ten-membered ring (still unknown) we again might expect low reactivity, since it possesses a closed electronic system. Therefore it would be interesting to attempt to synthesize this compound" [33, p. 255].

Now this completely conjugated ten-membered ring (cyclodecaptentaene, [10]annulene), which with its 10π-electrons is the "aromatic" homolog following benzene, evidently does not confirm the 4n + 2 prognosis, which is due to the stress on the ring and, correspondingly, to steric hindrances to coplanarity ([10]annulene can be produced only at −190°C) [170]. Only definite modifications of the structure, providing for the necessary flattening of the molecule, lead to stabilization due to conjugation in the 10π-electronic group. Such modifications are the presence of a bridge methylene, oxa- or aza-groups in the 1,5-positions of the framework of cyclodecapentaene (see the survey [171]), as well as iso-π-electronic

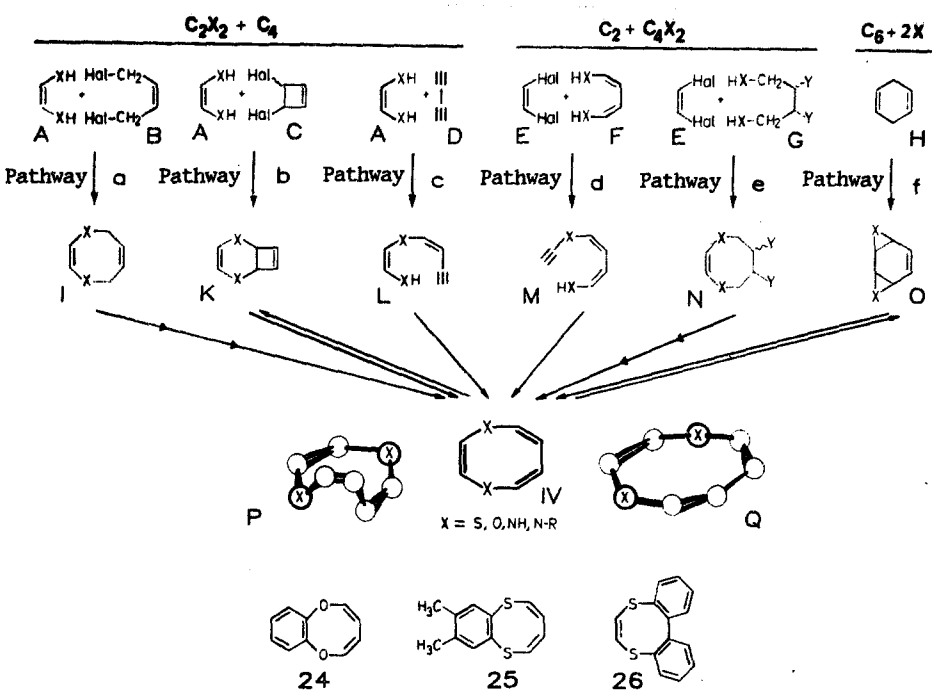

Fig. 12. Pathways of synthesis of 1,4-diheterocines (heterocyclic 10π-electron systems).

substitution of the C=C double bond by the carbanion site as a member of the ring with its simultaneous narrowing. The latter case is represented by the cyclononatetraenide anion [172-174] and the cyclooctatetraenide dianion [175-178], which can be depicted by formula 12-IV or 6-IV, X=CH⁻. Therefore it is natural to postulate that heteronins (hetero[9]-annulenes) and 1,4-diheterocins (1,4-dihetero[8]annulenes) 12-IV (X is a heteroatom) also possess a 10π-electron system [42, 108, 179, 180]. An important analogy is the iso-π-electronic relationships between the classical 500 heterocycles, the cyclopentadienide anion, and benzene in the 6π-series (see Section 1.2).

The question arose of the degree to which 1,4-diheterocin 12-IV (correspondingly 6-IV, X = O, S, N-R), as heterocyclic "pseudocyclodecapentaenes" with a 10π-electron system, exhibit "aromatic" properties according to the Hückel postulate (for the conceptual approach to the resolution of the question and the first communications, see [181, 182]). In this case the gain in energy of delocalization should be rather large, so that the increase in the valence angle was energetically compensated for by flattening of the π-system in the ring.

The program of synthesis provided for the production of eight-membered heterocycles as a result of two component cyclization ($C_2X_2 + C_4$ and $C_2 + C_4X_2$); moreover, the formation of new bonds occurs at the heteroatoms. The scheme of synthesis of 12-a (Fig. 12) is based on the reaction of cyclization between cis-1,2-diheterosubstituted ethene 12-A (cis-1,2-dimercaptoethene, o-substituted benzenes, for example, pyrocatechol, dithiopyrocatechol, 4,5-dimercapto-o-xylene, N,N'-dimethyl-o-phenylenediamine, etc.) and cis-1,4-dihalo-2-butenes 12-B, as a result of which a dihydrogenated eight-membered ring 12-I is initially formed. This step is followed by the introduction of the missing double bond (dehydrogenation, addition of a halogen, followed by elimination of hydrogen halide, etc.). According to scheme 12-b, the structural fragment C_4 is transferred with the aid of the 3,4-dihalocyclobutene 12-C, representing the "open" form of 1,4-dihalo-1,3-butadiene; the dicyclo[4.2.0]-octadiene derivative 12-K formed in this case remains to undergo electrocyclic valence isomerization. The methods of synthesis of 12-c and 12-d lead to a chain by "direct condensation": according to scheme 12-c, the dinucleophile 12-A, which is evitably a dimercaptide, is added to the 1,3-butadiyne 12-d; the reaction is regio- and stereodirected, as in the synthesis of cis,cis-1,4-dithiobuta-1,3-diene (compare with the production of the structural fragments 7-1 and 7-2 and heterocycles of the type of 6-II; section 2.1.2). Pathway 12d corresponds to "cyclovinylation" of cis,cis-1,4-dinucleophile-1,3-butadiene (compare with the principle of the approach to heterocycles of the type of 6-III, Section 2.1.3).

Other possibilities are reflected in schemes 2-e and 2-f: in the first case a definite parallel to the strategy according to pathway 12-a is considered. In comparison with compound 12-I, in the cyclization product 12-N there are substituents Y that are necessary for subsequent twofold elimination and were already introduced into the component for closing of the ring of 12-G (an increased tendency for opening of the ring might be expected according to the "principle of fixed groups," when the heterosubstituents themselves have already been incorporated into the ring, for example, in acetals, ketals; cf. [183, 184]). Pathway 12-f utilizes the "natural" cycloconversion $[_{\pi}4_s + {}_{\pi}2_s]$ the synthesis is oriented chiefly to the approaches to the valence isomer 12-O. As will be revealed below, this pathway proved to be the most fruitful in the synthesis of compounds of the 1,4-diheterocin series.

The method 12-a can be used in the synthesis of 1,6-benzodioxocin 12-24 [185], method 12-b for the production of 1,6-benzodithiocine 12-25 [186] (cf. also [108, 187]), and 12-d for the production of benzo-1,4-dithiocin 12-26 [188]. The results proved rather skimpy in comparison with the extensive expenditures associated with the preparation for the synthesis. For example, numerous dihydro compounds of the type of 12-I (X=O,S,N-R) and the corresponding nelated structures [110, 189, 190] could not be converted to structures of the type of 12-IV, since in this case such side reactions as opening or transformation of the ring predominate (see, for example, reaction 5-B; Fig. 5), due to the influence of heteroatoms on the neighboring groups. An approach to the type of 12-IV by direct condensation, in accordance with the schemes 12-c and 12-d, met with failure, since in this case rings with a number of members less than eight (for example, 1,4-dithiyne) are formed [188]: an exception is the case when the C=C double bond of the C_4X_2 component is fixed by the benzene rings (scheme 12-d: example 12-26); and, finally, unexpected anomalies are also detected in the implementation of scheme 12-b [108, 191, 192] (cf. also [193]).

In addition, cyclization, leading to 2-vinylhydro-1,4-benzodiheterynes (to a step of an intramolecular S_N2' reaction, while in the case of the reaction of exchange of pyrocatechol with cis-1,4-dichloro-2-butene, it leads to the formation of 1,2; 9-10-dibenzo-3,8,11,16-tetraoxacyclohexadeca-1,5,9,13-entirely cis-tetraene, a previously known analog of dibenzo-1,4-crown-4), competes with the formation of dihydro derivatives of 12-I.

From the aforementioned it can be concluded that 1,4-diheterocins of type of 12-IV are not characterized by the ease of formation that is typical of classic hetarenes, i.e., they do not possess sufficient stability under the conditions used. Actually, the properties of compounds 12-24 to 12-26 entirely contradict the criteria used for aromatic compounds. The UV spectrum of compound 12-24, especially in comparison with the spectrum of 1,4-benzodioxine [167], makes it possible to exclude conjugation of the oxygen atom with the benzene ring, which should indisputably have existed in the case of coplanarity of the heterocyclic portion of the molecule [185]. For all three compounds (12-24 to 12-26) the signals of the protons of the C=C double bond in the ^1H NMR spectra are situated in the "olefin region," just as in the spectra of partially hydrogenated compounds (for example, of the type of 12-I). Compounds 12-24 and 12-25 readily undergo photochemical dysrotatory rearrangement to the corresponding cis-derivatives of bicyclo[4.2.0]octadiene 12-K [108, 185, 187]. Even 12-24 reacts smoothly in a Diels–Alder reaction with dienophiles at the butadiene fragment [185], which is unusual for an eight-membered ring; hence if can be concluded that the achievement of the coplanarity of this portion of the molecule necessary in this case is not associated with large energy expenditures. As an argument in support of the aforementioned we might cite the relatively long-wave but weak UV absorption of compound 12-25 at 360 nm [186]. And yet, the data of x-ray crystallogrphic analysis give the latest evidence that in a crystal the compound 12-25 exists in a boat form 12-P and does not even approach the coplanar structure 12-Q; the bond length and bond angles entirely correspond to model olefins (for example, 1,3-butadiene itself), and the sulfur atoms do not participate in the conjugation [194].

Certain results outlined here coincide with the data obtained recently by other groups of researchers (1,4-dithiocins — [183, 184, 187, 195, 196]; 1,4-diazocines — [197, 198]; 1,4-dioxacins — [199, 200]; 4H-1,4-oxazocines — [180, 201-203]; higher heteroannulenes — [43, 179, 204, 205] [6]; also compare the syntheses according to schemes 12-b [187, 197], 12-e [183, 184]; in this case 1,4-dithiocinyl-6-acetate has a noncoplanar structure, as shown by the result of x-ray crystallographic analysis). 1,4-Dithiocins are converted through the valence isomers 12-O (X = S) to benzoid structures, readily losing sulfur [183, 184, 187, 196]. In contrast to "nonaromatic" 1,4-dithiocins 12-IV (X = S), the 1,4-dithiocin anion should be characterized by 10π-electron delocalization ("although the degree of aromaticity seems negligible" [206]).

Of course, the benzannelation existing in our case suppresses the valence isomerization to a tricyclic of the 12-O type, possible for structures of the type of 12-IV (X = O, S, N–R) and on account of side reactions of S-compounds, fraught with irreversible consequences. Benzannelation, however, greatly hinders conjugation, and consequently, flattening in the heterocyclic fragment of the molecule as well. Moreover, even without this, the reduced contribution of conjugation in the case of replacement of a C=C double bond by a 2π-heteroatom is decreased even more in the presence of two heteroatoms in the ring. The predictions based on the data of quantum chemical calculations are contradictory: contrary to the previously expected rather "aromatic" stabilization [207], calculations according to Hückel, using thermodynamically substantiated coulombic and resonance integrals, arrive at the conclusion that the type 12-IV, especially when X = S, does not posses any special electronic stability, and this "shows that the use of the Hückel rule for systems differing from monocyclic hydrocarbons involves a definite risk" [208]. The didactically and heuristically justified principle of iso-π-electronic substitution has ultimately reached its limits!

Certain results obtained recently for the first members of the series of 1,4-diheterocin [198, 201, 209, 210], especially after it was possible to carry out a general and rather effective synthesis of these compounds according to scheme 12-f using valence isomerization of the tricyclic 12-O, proved unexpected and impressive. Although 1,4-dioxacin [199, 200] and 1,4-dithiocin [183, 184, 196] are purely olefinic, 1,4-dihydro-1,4-diazocine and its N,N'-dimethyl-, N,N'-bis(trimethylsilyl)-, and N,N'-bis(dimethylcarbanoyl) derivatives unambiguously correspond to the criteria of 10π-aromaticity, among which we shall mention only a flat structure of the molecule. This circumstance seems simply stupefying, since according to the quantum chemical predictions, 1,4-dihydro-1,4-diazocine should be nonaromatic [211]. On the other hand, a purely olefinic character has been demonstrated for N,N'-bis(methoxycarbonyl)- and N,N'-dimesyl derivatives (distorted boat conformation). Comparable ratios, depending on the nature of the substituent, also exist among representatives of the 4H-1,4-oxazocine series [201]. Thus, if 10π-delocalization is subject to even the extremely fine influence of substituents, then it is surely influenced by benzannelation as well. An analogous situation, nonetheless, has also been noted for compounds of the axonine series, representing 10π-electronic systems with nine-membered heterocycles (cf. [180, 202, 203]).

2.1.5. Pseudoazulenes of the Type of 6-V

In compounds of the type of 13-V (corresponding to 6-V), the 2π-heteroatom X replaces a C=C double bond of a nonbenzoid aromatic hydrocarbon azulene 13-27 (Fig. 13). As a result of this, compounds of this kind — cyclopentane[b](hetero)pyrans — are called "pseudoazulenes" (oxalene X = O; thialene X = S; azalene X = NR) [212, 213]. In them, as in azulene itself, there is a possibility of formation of anionic and cationic 6π-systems, in accordance with the boundary form 13-Vb (compare with 13-27b).

Despite this circumstance, responsible both for the alternation of the π-charge density and reactivity with respect to electrophilic and nucleophilic agents and for the color of azulene, the presence of a transannular 9,10-bond in it is manifested only slightly in an aromatic equalization of the bonds in the groud state. We can thereby give an explanation for the observed bond length (1.458 Å) and the relatively low dipole moment (1.7 D). A high degree of stabilization by conjugation (resonance energy 192 kJ/mole) can be ascribed primarily to the 10π-electron system, delocalized along the periphery of the ring of the molecular framework. As a result of this, azulene is considered as [10]azulene, flattened on account of a bridge bond [214]. Analogously, pseudoazulenes can be considered bridge hetero-[9]annulenes (heteronins: oxonins, thionins, azonines) [180, 202]. "Aromatic" delocalization of the 10π-electrons in "nonbridge" heteronins, as in 1,4-diheterocins 12-IV, seems problematical (see Sections 2.1.4).

In the series of 1,2-benzoaxalene 13-29 there is a possibility for extensive investigations. The experimental basis for this was provided by the effective methods of synthesis of pyrylium salts [98-100] by [C_2 and C_3]-two-component cyclization (Fig. 13; see also Fig. 4). They consist of interaction of acylvinyl chlorides (β-chlorovinyl ketones) with enamines, leading to ketovinylenamines [215, 216], and cyclodeamination of the latter with the aid of acids (synthesis 13-A) [217], in direct ketovinylation of arylacetylenes or ketones by acylvinyl chloride in the presence of Lewis or protic acids (syntheses 13-B and 13-C) [218-220], as well as in the acid condensation of β-diketones with carbonyl compounds (synthesis 13-D) [221, 222] (cf. also [223-225]). Indeno[2,1-b]pyrylium salts 13-28, produced on the basis of 2-indanones or their enamines as a C_2-component, is reasily deprotonated with the forma-

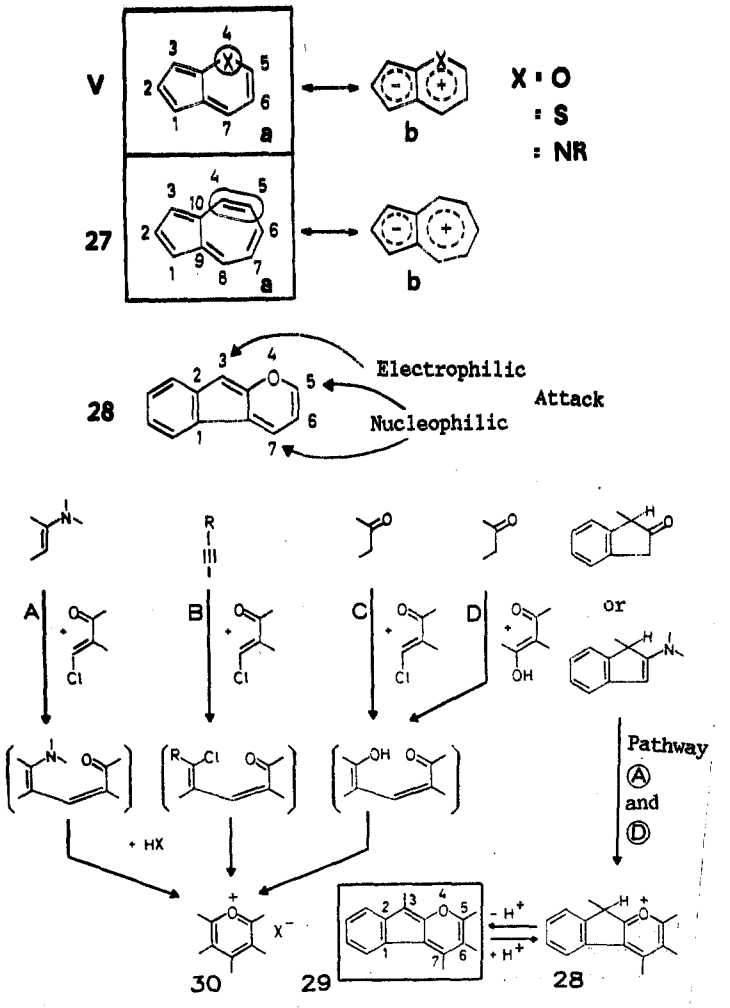

Fig. 13. Pseudoazulene of the type of cyclopenta[b](hetero)pyran. Regiochemistry of 1,2-benzoxalene with respect to electrophilic and nucleophilic agents. Syntheses of pyrylium salts and 1,2-benzoxalenes.

tion of 1,2-benzoxalenes 13-29: numerous representatives of this ring system, carrying various substituents, have become available in this way [226, 227].

1,2-Benzoxalenes of the type of 13-29 represent a heterocyclic structural analog of 1,2-benzazulene (for surveys of azulenes, see [228, 230]). Just as in the case of the latter, electrophilic substitution in the five-membered ring occurs with unusual ease ("enylation" according to C(5) with the aid of carbonyl compounds acylated according to Friedel-Crafts, formulated according to Vilsmeier et al.) [231]. Nucleophilic reactions proceed at positions 5 or 7 of the pyran ring (introduction of substituents with the aid of organolithium compounds). The results of the experiments are in good agreement with quantum chemical predictions of reactivity [232]. Optical shift rules important for compounds of the axulene series [228-230] have been substantiated here on the basis of extensive experimental material, and they have also been substantiated on the basis of the Hückel molecular orbital theory (dependence of N-V_1 transition on the nature of the substituents) [233]. The resonance energies established from the enthalpies of combustion and sublimation are correlated with the energies of delocalization, calculated according to the Hückel method (for example, 5,6,7-trimethyl-1,2-benzoxalene — 414 kJ/mole, 5-phenyl-1,2-benzoxalene — 502 kJ/mole, and 1,2;5,6-dibenzoxalene — 490 kJ/mole). Then 165 kJ per benzene ring, the resonance energy of 13-V (X = O), is deducted, in all cases a value on the order of 165-250 kJ/mole is obtained for the oxalene system itself [231], lying within the range of values found for azulenes [228-230], which confirms the high degree of stabilization by conjugation in heterocyclic structures. The results of subsequent physicochemical investigations were presented in [212, 213]; for information with respect to 1,2;5,6-dibenzo derivatives, see [234, 235] (in [235] there

are also opposite data for 1,2;5,6-dibenzoxalene, on the basis of the results of x-ray crystallographic analysis).

2.2. Supplement: Heterocycles Based on Acetylene — Carbonyl Analogs of the C ≡ C Triple Bond

The leitmotif of this topic was already outlined in Section 2.1, where it was indicated that acetylenes and their simple derivatives are frequently used as starting materials for further synthesis (see the surveys [236-241]).

Thus, 2-butyne-1,3-diol lies at the basis of the second step of the synthesis of cis,-cis-1,4-dimercapto-1,3-butadiene (through a stage of 1,4-dichloro-2-butyne and butadiyne), which is a precursor of systems 6-II and 6-IV (see Sections 2.1.1 and 2.1.4), and hydro-1,4-diheterocins 12-I (to a stage of cis-2-butyne-1,4-diol and cis-1,4-dichloro-2-butyne), on the basis of which possibilities of synthesizing heterocyclic [9]annulenes 6-IV are opened up, especially in the case of 12-25 (see Section 2.1.4). Acetylene is used analogously for the production 3,4-dichlorocyclobutene, which is then used in the synthesis of 12-K — by cyclic presursors of compounds of the type of 6-IV, in this case through cyclooctatetraene or 2-butyne (see Section 2.1.4). The use of vinylidene chloride or 1,2-dichloroethene opens the way for the synthesis of cis-1,2-dimercaptoethene and then to heterocyclics based on 1,2-dithioethene, corresponding to the types 6-I, 6-III, and 6-IV. Reactive intermediates are chloroacetylene and ethynylthioesters (see Sections 2.1.2-2.1.4). Acetylene itself or vinyl chloride is used for the production of acylvinyl chlorides (β-chlorovinyl ketones, see the surveys [242-245]), which are suitable for various reactions of heterocyclization and always permit the synthesis of pseudoazulenes 6-V, among which compound 13-29 is especially noteworthy. In addition, acylvinyl chlorides are widely used in the synthesis of pyrylium salts 13-30 (Section 2.1.5). The syntheses of heterocyclics through acylketene dichlorides (β,β-dichlorovinyl ketones), produced from vinylidene by acylation or from alkylvinyl esters on the basis of the addition of CCl_4, as described in the Sections 2.3 and 2.4, are also based on acetylene chemistry.

In this case the C≡C triple bond is a sort of "anhydride" of a carbonyl compound or enol; consequently, it plays the role of a latent carbonyl function (cf. [63-65]; the main conversion is classical hydration according to Kucherov). It should be considered that reactions in which carbonyl groups participate lie at the basis of numerous syntheses of heterocycles. As a heuristic concept, we can consider the "chemistry of pseudocarbonyl compounds" based on alkynes useful for the synthesis of heterocyclics: instead of carbonyl condensation, heteronucleophilic addition to the C≡C triple bond, equivalent to vinylation at the heteronucleophilic reaction site, is used. The chemical accessibility of alkynes and the possibility of their modification permit various pathways of synthesis to be carried out, bypassing the carbonyl stage (see Fig. 14, part A).

The main problem is the regioselectivity of nucleophilic attack, and therefore the structure of the carbonyl equivalent also proves important, along with the entire aggregate of varied factors that can affect the course of the reaction (the effects of substituents size of the ring, intra- and intermolecular interactions, reaction conditions, etc.).

An example demonstrating the relatively assured prediction is provided by "cyclofunctionalization" of ethynyl ketones with dinucleophilic agents, which usually play the role of 1,3-dicarbonyl equivalents (see Section 2.4). The situation proves more complex in the case of acetylenes with heterosubstituents at the terminal carbon atom. For example, chloroacetylene reacts with dimercaptans, forming 1,2-dithioethene heterocycles ("cyclovinylation," cf. Section 2.1.3), whereas in the interaction with diols, cyclic 2-chloromethylacetals are obtained [246]. Both reactions of ring closing, of course, equally reflect the synthetic equivalent of 2-heterosubstituted carbonyl compounds, the former, however, in a sense of reactivity at the 1,2-position and the latter at the 1,1-position (see Section 2.4, in which it is shown that vinylidene chlorides play the role of 1,2- or 1,1-reagents, depending on the influence of substituents).

It is well known that heterosubstituents at the terminal carbon atom, despite the similar π-donor effect, have different orienting effects (Fig. 14, part B, cf. [247]): in compounds of the X—C≡CH type, the heteroatoms (X = N, O, and F) act as α-orientors (deactivation of the β-position), while representatives of the following periods (X = S, P, Cl, Br , etc.) act as β-orientors (joint manifestation of a decreasing π-donor effect and of stabilizing influence of X atoms on the negative charges). Usually differentiation occurs

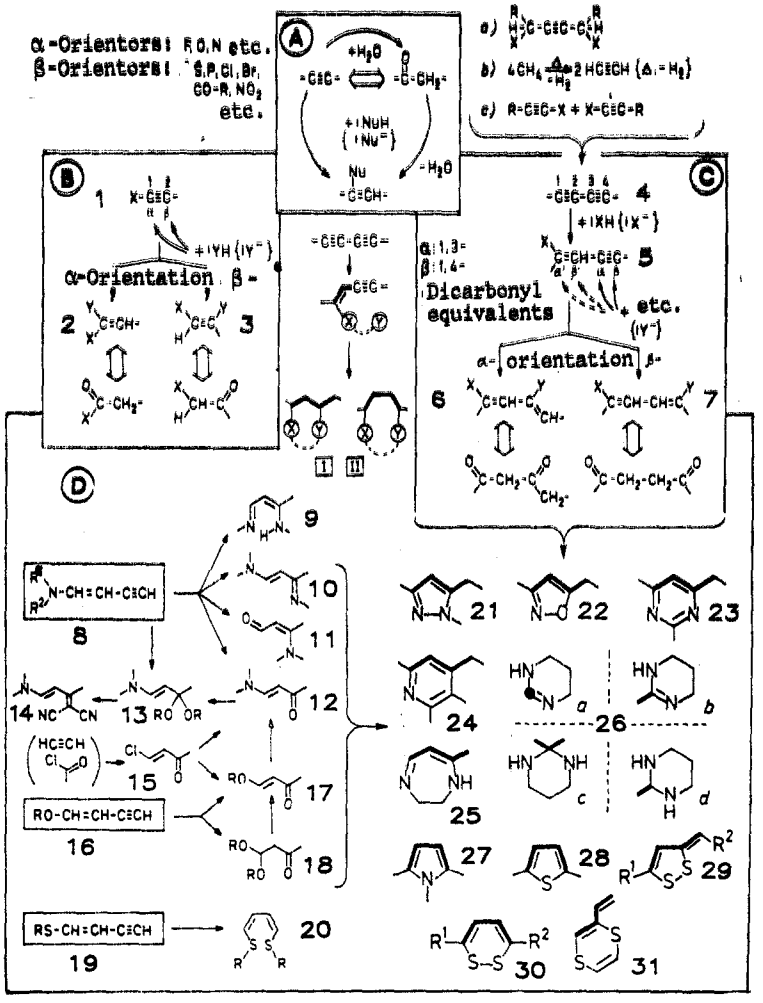

Fig. 14. Synthesis of heterocyclics based on acetylene.

under conditions of active catalysis; in this case there is a nucleophilic α-addition (electrophilic attack initially at the β-position, then activation of the conjugated acid). π-Acceptors substituents in all cases promote nucleophilic β-addition (substituents: COR, NO_2, etc.). Of course, these orientation rules are determined primarily by electronic effects and do not consider the influence of other factors (regiosynergism and regioantagonism can be considered as a special problem in the case of disubstituted acetylenes).

The heuristic principle under consideration became evident primarily in the butadiyne series (Fig. 14, part C)*: butadiones 14-4 are undoubtedly equivalents of dicarbonyl compounds and in this respect are of special interest, since dicarbonyl compounds seem to be designed precisely for varied syntheses of heterocyclics (see Section 2.4).

The development of industrial synthesis has promoted the unflagging interest in studies with butadiynes, in the broad meaning of the word — with conjugated polyynes (see, in particular, the surveys [237, 238, 240]): the approach to acetylenes is based on double dehydrochlorination of 1,4-dichloro-2-butynes, namely, on conversions arising in the ethynylation of aldehydes of 1,4-dihydroxy-2-butynes, in the simplest case, 2-butyne-1,4-diol, which is of great technical importance. Let us note that butadiyne is a side product in the industrial production of acetylene by the cracking of methane (dehydrodimerization of acetylene). Furthermore, we should have indicated different variants of the widely used C,C-bonding for monsubstituted alkynes (see, in particular, [237, 238, 240]). The development of butadiyne chemistry is also associated with the biogenesis of conjugated polyynes; thus, many hundreds

*Primarily studies conducted in the author's laboratory have been used as illustrative material, as already indicated in the introduction to Section 2. Soviet researchers have also made a special contribution to the coherent development of butadiyne chemistry; an extensive bibliography is presented in the surveys [238-240, 248].

of compounds with an alkyne structure, contained in plants, have become known, together with heterocyclic and other products of their conversions (see [236, 237, 241]).

In reactions with nucleophilic agents, butadiynes act as alkynes activated by acceptors (electronegativity of the ethynyl group), which is characteristic in general of conjugated polyynes. As a result of this, nucleophilic addition occurs primarily at the terminal position (under the action of basic catalysis) and leads to the formation of 1-heterosubstituted 1,3-butenynes 13-5. The C≡C triple bond remaining in these compounds opens up the possibility for repeated nucleophilic attach at positions 3 and 4 [247, 248]; thus, as a result of two steps of vinylation, heteroanalogs of 1,3- and 1,4-dicarbonyl compounds or their enols are formed.

The primary addend X introduced into compound 14-5 at the same time determines the regiodirection of repeated nucleophilic addition. Usually substituents X in compounds 14-5, representing amino or alkoxy groups, promote the occurrence of the reaction at position 3 (α-orientation with the formation of 14-6), while thiosubstituents promote a reaction at position 4 (β-orientation with the formation of 14-7). Depending on the nature of the primary adduct, butadiynes can consequently act as 1,3- or 1,4-dicarbonyl equivalents. The full correspondence to the principles of orientation operating in the case of heterosubstituted compounds 14-1 becomes evident (cf. [249]); 1-heterosubstituted 1,3-butenynes 14-5, in turn, act as vinylogs of compounds 14-1 (14-6 is similar to 14-2, while 14-7 is similar to 14-3). Analogously, the principle of vinylogy is also observed in the case of acid catalysis, when π-donor substituents X in compounds 14-5 direct repeated nucleophilic attack chiefly at position 3, and in certain cases at position 1, equivalent from the standpoint of the reaction mechanism (α- or α'-orientation).

Heterodinucleophilic agents are capable of reacting successively with butadiyne to form heterocycles; in this case the principles of orientation of bis-addition, leading to acyclic systems, should be preserved.

In other words, depending on the nature of the primary addend X in compounds 14-1, butadiyne can play the role of a transporter both of a triatomic and of a tetraatomic carbon fragment of the ring (of the type of 14-1 or 14-11).

Several examples can be cited (Fig. 14, part D), showing graphically that the reactions of nucleophilic addition to the primary products 14-8, 14-16, and 14-19, with the formation of open systems can be considered as model reactions. The interaction of N-monosubstituted 1-amino-1,3-butenions 14-8 with primary aliphatic amine leads as a result of exchange of amino groups to potentially tautomeric aminocrotonaldimines 14-9, which are also formed in one step directly from butadiyne (only in the case of tert-alkynes can monoaddition products of the type of 14-8 be recorded); on the contrary, arylanines are added exclusively with the formation of compounds of the type of 14-10 [249-250]. Depending on the reaction condition, the hydration of compounds 14-8 yields primarily β-aminocrotonaldehyde 14-11 or β-aminovinyl methyl ketone 14-12 (isomerization) [251]. The addition of alcohols, catalyzed by bases, leads to vinylogs of amidoacetals 14-13 [251, 252], which, just as we should have expected, react with CH-acids (example 14-14). It is noteworthy that under analogous conditions 1-alkoxy-1,3-buteniones 14-16 are converted primarily to C_1 adducts (the result of the acceptor influence of the ethynyl group), subsequent hydration of which ultimately leads to β-keto-acetals 14-18, while thermolysis leads to β-alkoxyvinyl ketones 14-17 (see [238]). The approach to compounds 14-12, 14-17, and 14-18 through the stage of β-chlorovinyl ketone again reveals their relationship to acetylene [242-245] (see Sections 2.1.5 and 2.3).

The reactions of formation of 1,4-diorganylthiobutadienes 14-20 through the stage of 1-organylthio-1,3-butenynes 14-19 (cf. Section 2.1) are characterized by 1,4-orientation, which is observed even in the addition of mercaptans to 1,4-dialkyl- or 1,4-diarylbutadiynes. Reaction products of this kind can also be obtained readily from 1,2-diaroylethames through the intermediate step of bis(diethylthio)acetal [253]. These circumstances once again explain the synthetic equivalence of butadiynes and 1,4-dicarbonyl compounds.

Let us note that in addition to terminal bonding, many other comparative possibilities are opened up for N-monosubstituted 1-amino-1,3-butenynes 14-8; thus, for example, compound 14-8 behaves as a synthon for nucleophilic introduction of a 4-aminobutyl group in the course of successive C-alkylation and hydrogenation with the formation of N-monosubstituted 1-aminoalkynes (compare with the data of [238, 252, 254]). It is most important that acyclic bis-addition products with an open chain (primarily 14-12, 14-17, and 14-18), representing

"functionally masked" 1,3-dicarbonyl compounds, are an important stage in the synthesis of heterocycles (see Section 2.4); in addition, the possibility is opened up for using them (especially those of the type of 14-18) as a storage form of butadiyne, which is technologically important.

In a consideration of the reaction of double nucleophilic addition, which leads from butadiyne directly to heterocyclic, various supplementary pecularities become evident; thus, the conditions of the reaction in which butadiynes themselves, as well as representatives uniformly disubstituted at the terminal position, participate are relatively unproblematical like the cases when we might expect the formation of hetarynes as reaction products.

Just as for the model reaction with the formation of acyclic double addition products, when N-dinucleophilic agents are used, reactions of ring closing, oriented in positions 1 and 3, predominate, for example, in the interaction with hydrazines, hydroxylamine, guanidines, or various enamine derivatives (primary N-nucleophilic influence): The formation of nitrogen-containing heterocyclics (pyrazoles 14-21, isoxazoles 14-22, pyrimidines 14-23 or pyridines 14-24) reflects the general picture for reactions of 1,3-dicarbonyl compounds [238, 239, 250, 255]. Heterocyclization with 1,2-diaminoethane, leading to the formation of 2,3-dihydro-1,4-diazepines 14-25 [255, 256], also fits into the same framework. Such addition is based on the occurrence of a side reaction, since in the normal course of the process, N-heterocycles with a larger number of links in the ring should have been obtained: in practice the interaction of butadiyne with 1,3-diaminopropane leads not to the expected eight-membered ring but, as a result of cleavage of a C–C bond with the formation initially of products of 1,3-bis-addition of the type of 14-9, to tetrahydro- and hexahydropryidenes 14-26 [257]. On the contrary, the synthesis of pyrrole 14-27 with multiple variations of the substituents on the basis of butadiyne and ammonia or primary amines in the presence of copper(I) salts (1,4-dicarbonyl equivalents) occurs according to a different mechanism from dinucleophilic addition [238, 239, 258]. On the other hand, the prediction is justified with respect to 1,4-orientation in the reactions with H_2S or Na_2S, leading to the formation of thiophenes 14-28 (primary S-nucleophilic attack) [238, 239, 259]. The formation of dithiafulvenes 14-29 instead of the 1,2-dithiones 14-30 [260] under the influence of Na_2S_2 [see the stepwise synthesis through the stage of cis,cis-dimercapto-1,3-butadiynes 14-20 (R = H), Section 2.1.1] is an exception; of course, the deciding role in this case is played by the supplementary ethynyl groups (R^2 = –C≡C–R). Reactions of cyclization in which cis-1,2-dimercaptoethenes (as well as their benzene analogs) participate, resulting in the formation of 2-vinyl-1,4-dithiyns 14-31 [188], graphically demonstrate that although 1,4-addition with the formation of an eight-membered ring (1,4-dithiocines) does not occur, contrary to expectation, nonetheless a mechaistically equivalent 1,2-orientation is observed (α'-orientation; see also Baldwin's rule for stereroelectronically directed reactions of ring closing [261], as well as the discussion in the article [247]).

In accordance with the well-known principles of natural science, in complex cases the situation should be treated in basic outlines and simplified to the maximum possible degree ("Occam's razor"). Guided by this, we have concentrated our attention only on selected examples, expecting that the remaining contradictions will be used for the explanation and demonstration of the causes of mechanistic alternatives. And finally, one last but no less important thing. We should mention that the development of work economics is speeding up the process of development of acetylene chemistry. Although acetylene has gradually lost its industrial significance as a basis for synthesis on an international scale, as evidenced by the low level of its production in the middle of the sixties, still it can be asserted without exaggeration that the use of the C≡C triple bond remains extremely important in the laboratory practice of organic chemistry. Moreover, we can now speak directly of a vigorour rebirth of synthetic organic chemistry, in which the outstanding reactivity of the C≡C triple bond is widely utilized. These trends should also promote the development of certain lines of the chemistry of heterocyclics.

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