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

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2.3. Chemistry of 1, 3-Thiazines; the Heterocyclic System and Its Synthetic Possibilities

The motivation for this review was a brief but challenging remark on the reaction of benzoylketene dichloride (β, β-dichlorovinyl phenyl ketone) with thiourea ([242], p. 189): "Thiourea and phenylthiourea form intensely colored soild products of unknown structure." It turned out that the reference was to 2-amino-1,3-thiazine-6-thiones [263-265] (see also [266]). Their formation opened a promising route of theoretical and synthetic interest to fully conjugated cyclic, 1, 3-thiazine systems. Some of the results obtained since then are based on the investigations of [267-277].

2.3.1. 1,3 Thiazine Type Structures

The fully conjugated 1, 3-thiazine ring is composed only of sp^2-hybridized atoms (hydrothiazines will not be considered here); its derivatives can be broadly subdivided into compounds with continuous cyclic conjugation and those with cross-conjugation (with exocyclic double bonds) corresponding to principal types 15-I and 15-IV of Fig. 15. The 1,3-thiazinium cation is the prototype, and the 1,3-thiazinemethides, thiazinones, and other heteroanalogs (with the 1,3-thiazinium cation as polar canonical form) are 6π-electron systems; thiazine anions and radicals must be considered as active intermediates. We combine 1,3-thiazines with 1,3-oxazines and 1,3-diazines (pyrimidines) into one "1,3-hetazine" series. Since 1,3-thiazine salts can also be considered as 3-azathiopyrilium salts, it is appropriate to compare them with pyrilium and thiopyrilium salts. The introduction of a nitrogen atom into the ring increases the positive charge on the ring carbons (π-deficit character), while the replacement of an oxonium atom by sulfonium decreases that charge; in their acceptor activity 3-azathiopyrilium salts (3-azathiopyrones) lie between pyrilium (pyrone) and thiopyrilium salts (thiopyrones). This also follows from charge distribution calculations by the CNDO/2 [278].

While thiopyrilium derivatives can often be obtained only by an indirect route, via pyrilium compounds by the action of H_2S [98-106, 278, 279] (for an exception see [280] and Sections 5.8.1.1 and 5.8.1.2 in the review [279]), as a rule 1,3-azathiopyrilium derivatives (1,3-thiazinium salts) form easily from available sulfur-containing reagents by direct cyclization by various convenient routes. Along with the multiple reactivity this creates all conditions needed for the use of 1,3-thiazinium derivatives as a synthetic "turntable" (see Section 1.3). If we take into account their structural kinship with "veteran" types like pyrimidines and 1,3-thiazoles (azalogy or carbenium homology), members of which play important roles in biological processes, it is legitimate to expect biological activity also in the 1,3-thiazines (the most impressive example in the hydrothiazine series is cephalosporin [281]). One can only wonder that the fully conjugated 1,3-thiazine system has been until quite recently an "outsider" and only very lately has come to the foreground of general interest [161, p. 488; 282-287].

2.3.2. Approaches to 1,3-Thiazines

Sixty-three different variations of 1,3-thiazine ring synthesis can be represented, specifically 6 one- and five-component, 15 two- and four-component, 20 three-component combinations and also (hypothetically), one six-component variant. Figure 16 shows graphically general descriptions of one- and two-component syntheses based on successive skeletal dis-

*For Part I, see [262].

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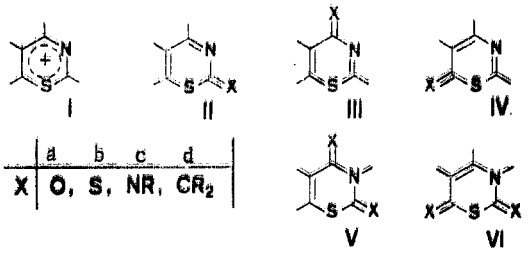


Fig. 15. Principal types of fully conjugated 1,3-thiazines.

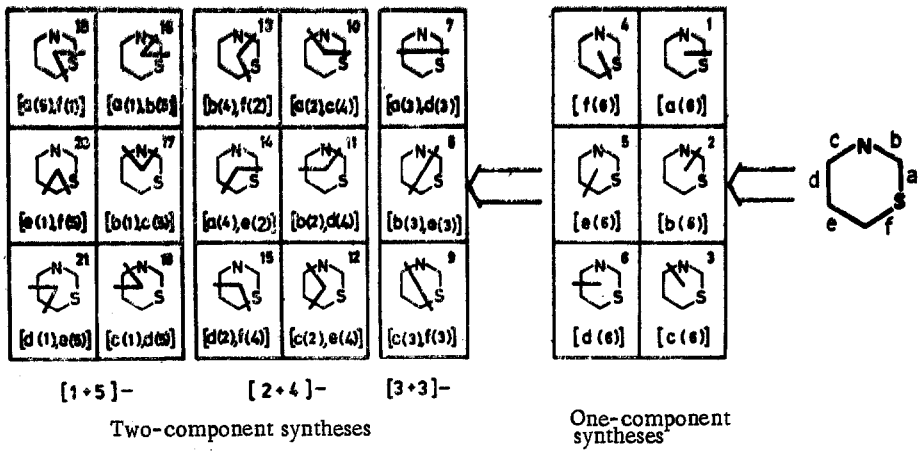


Fig. 16. Combinations of structural fragments in 1,3-thiazine synthesis; retrosynthetic illustration for one- and two-component syntheses.

membernent ("scission"). Here we use the Patterson notation for describing rings, in which letters of the alphabet stand for places of bonding or scission, and numbers in parenthesis stand for the number of atoms in each of the structural fragments to be combined. In theory, however, all synthetic approaches, if they are not (synchronous) multicenter cyclizations, ought to come down to one-component ring closure reactions (see also the analogous situation in pyrilium salts [98, 99]; the notation is taken from the book of [106]).

Often the principal step of a synthesis is "direct condensation" of two reagents, although individual steps may precede the formation of these structural fragments. With the help of Fig. 17 let us consider some typical examples. The reaction of 2-aminocyclopentene-dithiocarboxylic acid with carboxylic acid derivatives give 4,5-trimethylene-1,3-thiazine-6-thione (line 17-1) [288] — a two-component synthesis of the [a(1), b(5)] type. The [b(5)] component (the NC_3S fragment) is obtained from cyclopentanone ([c(2)] fragment), ammonia ([b(1)] fragment), and carbon disulfide ([e(2)] fragment) [289, 290]; the [a(1), b(5)] two-component condensation to 1,3-thiazine-6-thione is expanded to an [a(1), b(1), c(2), e(2)] four-component synthesis. In the second example (line 17-2) the same 1,3-thiazine-6-thione forms from 2-dichloromethylenecyclopentanone (acylketene dichloride as the [c(3)] fragment of the synthesis) and a thioamide (NCS component as the [f(3)] fragment) [263-265]. If, however, we take into account that 2-dichloromethylenecyclopentanone is obtained from cyclopentanone (the [c(2)] fragment of the skeleton) by conversion to enamine and reaction with CCl_4 ([c(1)] fragment) [291, 29]], then the [c(3), f(3)] two-component synthesis is expanded to a [c(2), e(1), f(3)] three-component synthesis. In the third example (line 17-3) we start from an acid chloride as the [c(1)] fragment of the thiazine ring. Reaction with acetylene (or with vinyl chloride, a [d(2)] fragment) gives acylvinyl chloride (the [c(1), d(2)] and [c(3)] components respectively [242, 243], which is converted by thioamide to a 1,3-thiazinium salt. The [c(3), f(3)] two-component condensation amounts to a [c(6)] cyclization, the fixed intermediate formation of ketovinyl ester of the thioimidoacid is introduced separately. Finally in the fourth example (line 17-4) we see a [c(3), f(3)] two-component reaction and correspondingly [f(6)] cyclization to 1,3-thiazine-4-one [269, 284, 293].

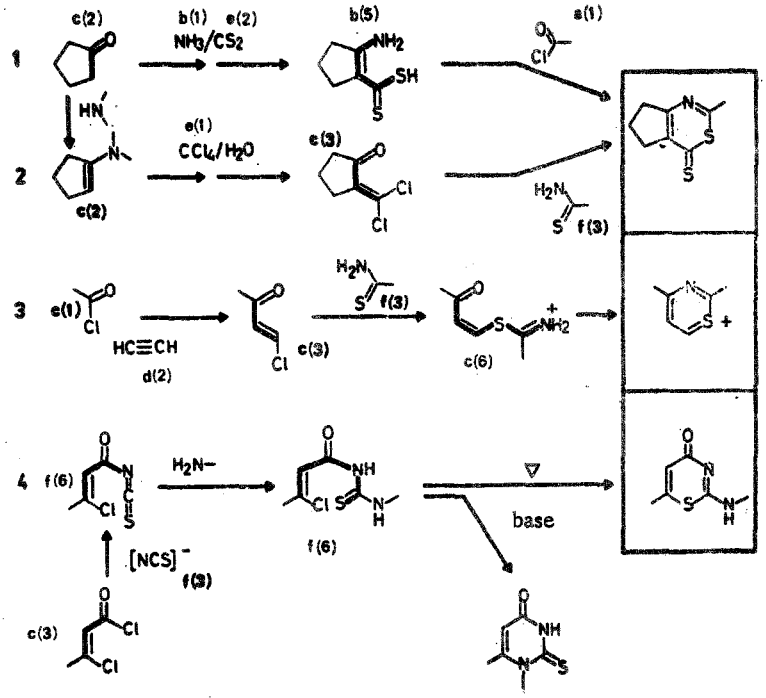


Fig. 17. Examples of 1,3-thiazine synthesis by combination of various structural fragments.

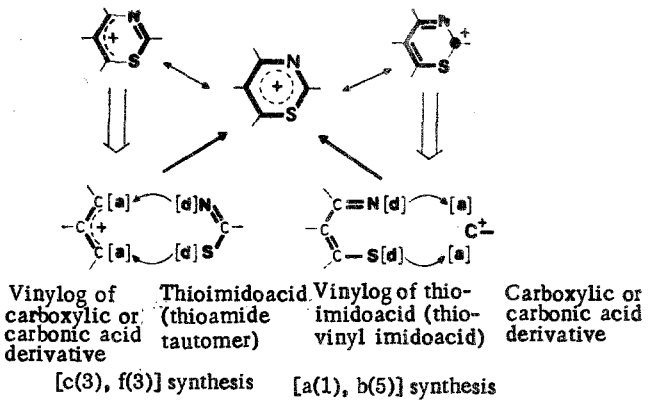


Fig. 18. Scission of 1,3-thiazinium cation to structures with charge localization in combination with synthones.

The significance of this discussion lies in the selection of a combination of structural fragments as a foundation for standardizing the route of heterocycle synthesis. The other decisive and nearly universal possibility lies in the functionality of the structural fragments (see Section 2.4). As Fig. 18 shows, depending on hypothetical charge localization the 1,3-thiazinium cation can be represented either as a carbenium ion captured by thiovinimide, or as an allyl cation closed into a ring by thioimide (for the "vin" terminology for vinylic systems, see [294]). Thus as already shown for example 17-1, for an [a(1), b(5)] two-component condensation we need to use a C_1 functional fragment that has at least three potential "carbon–heterocycle" bonds (derivatives of carboxylic and carbonic acids). Very much broader synthetic possibilities are opened by the [c(3), f(3)]- or [C_3 + NCS] two component condensations shown in the second example; here the thioamide function (generally the NCS fragment reacts prototropically with the thioimidoacid) forms a ring by using a 1,3-bifunctional allyl cation as a C_3 fragment. The latter can be conjugated acids of β-dicarbonyl compounds of their synthetic equivalents (acylvinyl chlorides, β-chlorovinylmethyleniminium salts; cf. diagrams in Section 2.4).

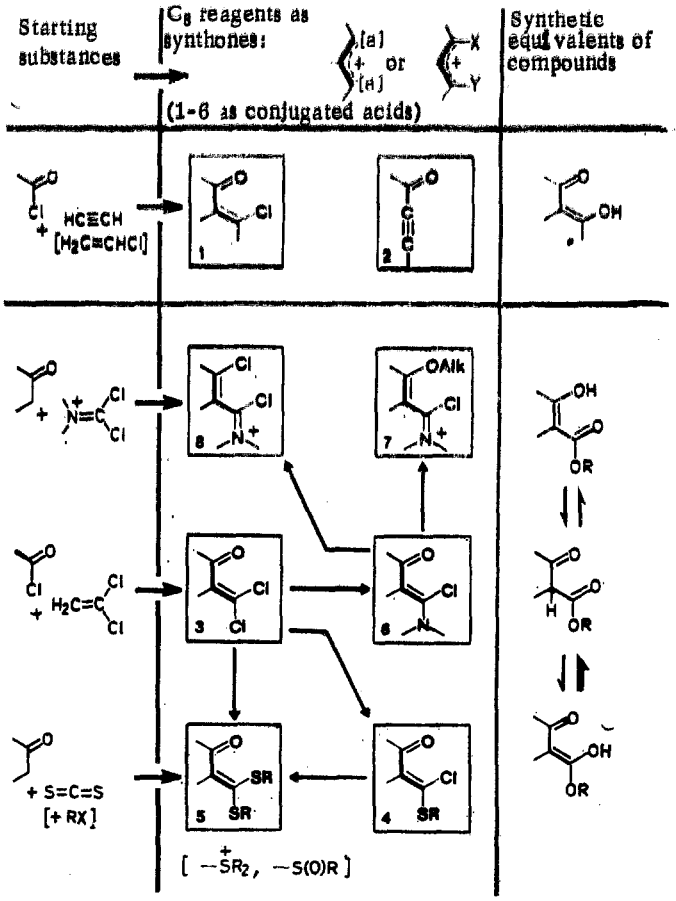


Fig. 19. C_3 reagents from acylketene dichlorides.

In [c(3), f(3)] and the corresponding [C_3 + NCS] two-component condensations, the choice of C_3 reagent is decisive. The circumstance that the synthesis of the [c(3)] thiazine fragment is essentially a 1,3-thiazine synthesis is responsible for the wide variability of synthetic possibilities and products. Figure 19 shows some suitable C_3 fragments, e.g., acylvinyl chlorides 19-1 (β-chlorovinyl ketones [242-245], cf. also 17-3) or acylacetylenes 19-2 (cf. Section 2.2) which have the same oxidation state as β-dicarbonyl compounds. The ackylketene dichlorides 19-3 (β, β-dichlorovinyl ketones [242-245], cf. also 17-2) also belong here; they are especially promising for preparative work. They can be used to obtain heterosubstituted final products either directly or after partial modification. Here we should note the intermediate conversion to α-chloro-β-acylvinyl sulfides 19-4 [295], acylketene mercaptals 19-5 (sometimes requiring additional activation via S-alkylation or S-oxidation [295, 296]), α-chloro-β-acylenamines 19-6 [297], β-alkoxyvinyl chloromethyleniminium 19-7, or β-chlorovinyl chloromethyleniminium salts 19-8 [297]. It was noted that compound 19-6 is alkylated at the carbonyl oxygen, whereas 19-4 and 19-5 on the contrary are alkylated at the heteroatom in the vinyl position [275, 296, 298]. The C_3 fragments 19-3 - 19-8, in spite of the difference in their functionality, are all synthetically equivalent to β-ketocarboxylic acids; they are as it were β-keto acids "retooled" with other hetero substituents. At the same time the β-keto acids and their esters, according to present information, are as a rule unsuitable for preparative [C_3 + NCS] cyclization. Various types of 19-5 and 19-6 compounds can be obtained also from methylene ketones and hydrogen sulfide (cf. Section 2.5) or from phosgene immonium chloride [299, 300]; this furthers broadens the choice of starting materials for C_3 components in 1,3-thiazine synthesis.

Practically all compounds with a thioamide function are suitable as the NCS component in cyclization, and the choice is determined here only by availability. Besides thioamides one can use thioureas, oxalate thioamides, thiocarbamic and dithiocarbamic esters, dithiocarbamate salts, thiosemicarbazides and thiosemicarbazones, etc. Figure 20 shows a schematic diagram of many efficient [C_3 + NCS] thiazine syntheses [263-265, 267-277, 295-298, 301-305]

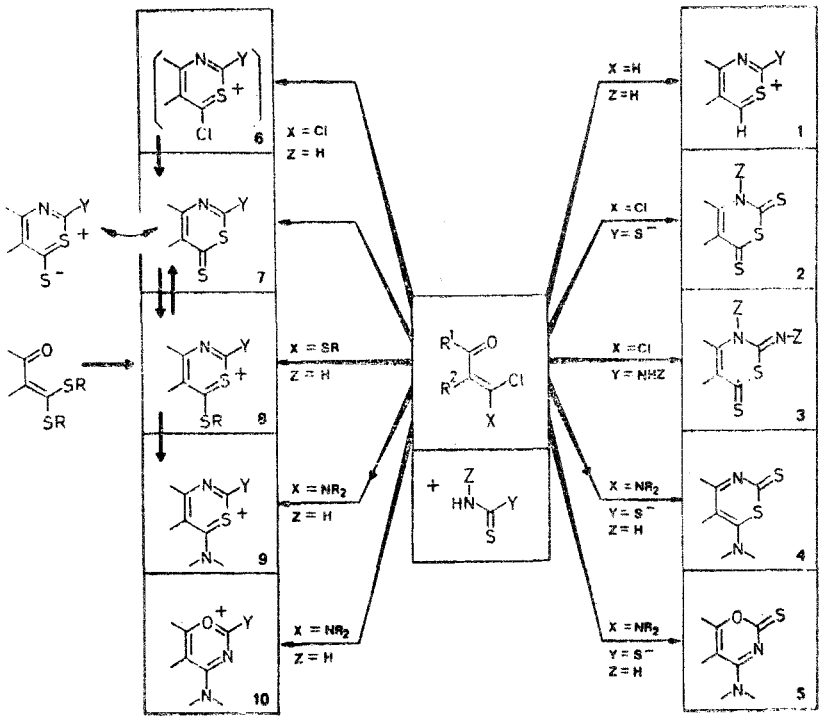


Fig. 20. Synthesis of 1,3-thiazines and 1,3-oxazines from acylvinyl chlorides and acylketene dichlorides.

that are characterized by a relatively strong tendency to form a completely conjugated 1,3-thiazine ring, including alternate cyclization to pyrimidinethiones (e.g., in the reaction of C_3 components with thiourea). Obviously the result of cyclization is predetermined by the primary attack of the C_3 component at the thioamide sulfur. In some cases, e.g., when acylvinyl chlorides react with thioamides or thioureas to form 20-1 [301], the primary products are separated and cyclized by a special procedure in the removal of water (cf. reaction 17-3) [302]. This result deserves attention because ketovinylation can be considered as "the vinylog of acylation" (cf. Section 2.4), and acylation of thioamides, including thiourea, under thermodynamically controlled conditions always gives N-products (as is known) [306-308]. Now for ring closure it remains only to form a C—N bond. On the other hand, by creating specific reaction conditions one can direct the heterocyclization to either 1,3-thiazine or pyrimidine structures, if by virtue of certain structural circumstances ring closure can proceed to form either a C—S or a C—N bond (e.g., reaction 17-4) [284]. One other condensation variant is known that forms 1,3-oxazine rings like 20-5 or 20-10 [275, 298] (in contrast to the related N-monosubstituted 4-amino-1,3,5-oxadiazine-2-thiones [309], the 20-5 compounds do not spontaneously convert to 1,3-thiazine-2-one derivatives). The chlorine substitution products that first form from α-chloro-β-acylenamines 19-6 isomerize most easily with acyl migration (cf. [297]). This competing reaction is hindered by O-alkylation of the C_3 component (to 19-7) mentioned above. Therefore only the respective 1,3-thiazine derivatives 20-4 and 20-9 ought to form thereafter. Similarly intramolecular acyl migration does not appear in the primary ketovinylation products when β-organylthio-β-chlorovinyl ketones 19-4 and acylketene mercaptals 19-5 are used; without complications the reaction gives 6-organylthio-1,3-thiazinium salts 20-8 [296, 301].

In the cyclization of acylketene dichlorides to 1,3-thiazine-6-thiones of the 20-7 type via the intermediate 20-6 we can recognize the formation of "the intensely colored solid products of unknown structure" already mentioned in Section 2.3, but now as a special case (cf. also reaction 17-2) [263-265], where the thiocarboxylic acid group forms by participation of a second thioamide molecule as sulfur carrier. The same route yields 2,5-disubstituted 1,3-thiazine-6-thiones from β, β-dichlorovinyl aldehydes and thioamides [274, 303]. Finally, the same principle of the "concurrence of cyclization and thiolysis" is followed in the reaction of acylketene dichlorides with thiocarbamic acid derivatives (ammonium dithiocarbamate, N,N'-dialkylthioureas) to form 1,3-thiazine-2,6-dithiones 20-2 or their 2-imino analogs 20-3 [269, 272, 277, 304].

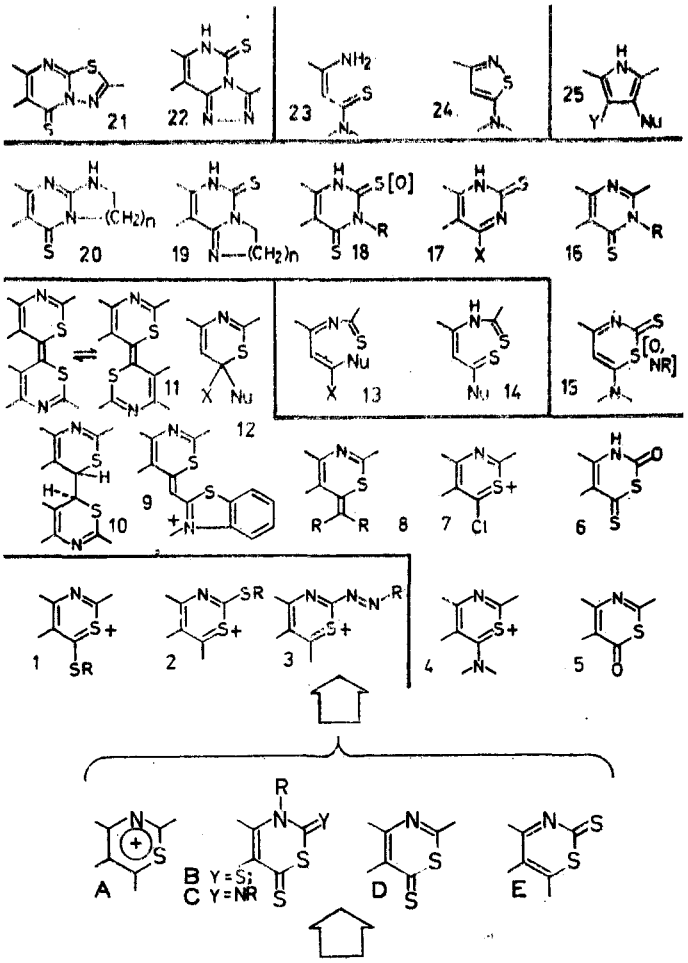


Fig. 21. Synthetic possibilities of fully conjugated 1,3-thiazines.

The variants of 1,3-thiazine synthesis presented here permit the substituents to be widely varied. Following are convenient approaches to 1,3-thiazine derivatives with various functional substituents or with no substituents in the reactive positions; such compounds seem to be destined for use in synthesis.

2.3.3. Reactivity of 1,3-Thiazines

The preparative properties of fully conjugated 1,3-thiazine systems are characterized chiefly by nucleophilic addition, nucleophilic substitution, ring scission and destruction, ring transformation, removal of sulfur from the ring, reductive dimerization to form a C—C bond, etc. (cf. the diagrams in Section 1.3). The synthetic value of this group of reactions lies in their broadening the possibilities of exocyclic transformations of substituents, mainly by the action of electrophilic reagents. Nucleophilic attack is directed predominantly at ring positions 2, 4, and 6.

Localization energies for nucleophilic addition to an unsubstituted 1,3-thiazinium cation calculated by the CNDO/2 method give reason for expecting reactivity to decrease in the sequence $C_{(2)} > C_{(4)} > C_{(6)}$ [278]. It is true that the energy differences are small, so that other factors that determine regiochemical behavior can appear (substituent effects, reaction conditions for kinetic control). Ultimately the outcome of the reaction is decided by the steps after the primary nucleophilic addition. In various cases a conclusion about primary nucleophilic attack at position 6 can be drawn from the study of the process results.

A series of examples is correlated by the diagram in Fig. 21 [268, 269, 272-277]. Compounds 21-1 - 21-3 represent exocyclic conversions of substituents. Thus 21-1 and 21-2 show alkylation or arylation of the respective 1,3-thiazinthiones (21-D and 21-E) [264], while 21-3 demonstrates conversion to an azo dye. Examples 21-4 — 21-12 show formation of a bond

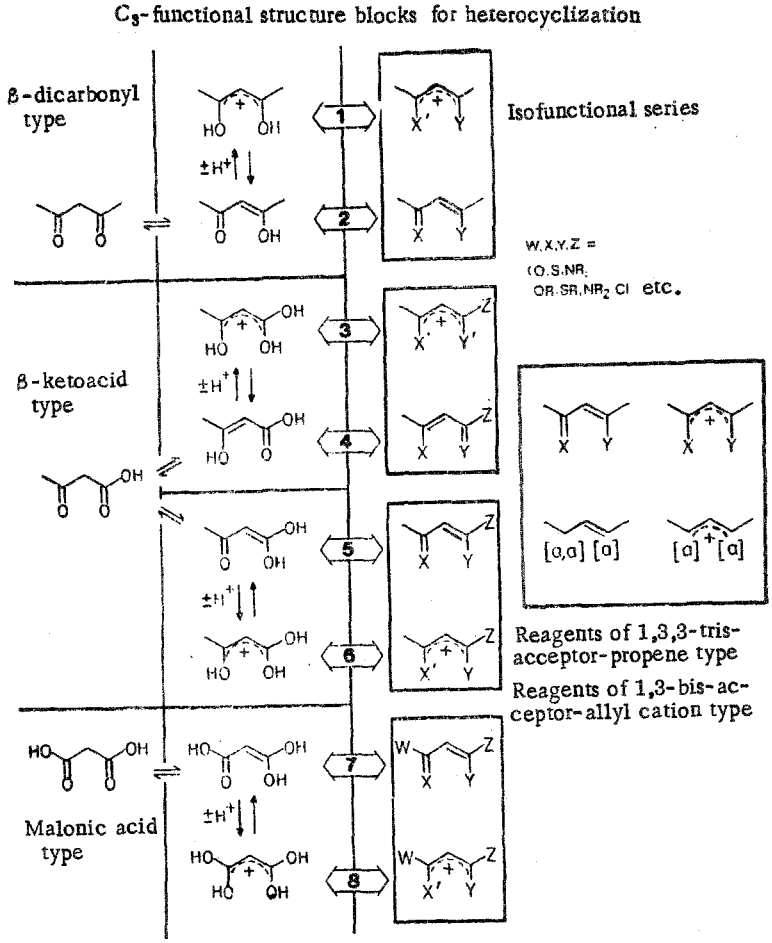


Fig. 22. C_3-functional structure fragments of β-dicarbonyl and β-keto-carboxylic and malonic acid types for heterocyclization.

with the thiazine ring: In 21-4 an SR group is replaced by a secondary amino group; 21-5 and 21-6 arise by detachment of a thiocarbonyl sulfur or hydrolysis of an alkylthio group; 21-7 is obtained by chloroiodolysis of the respective thiazines, 21-8 comes from alkylthio-1,3-thiazinium salts and active methylene compounds (R = CN, COR, COOR, etc.); the methyne dyes 21-9 form by the same principle. Moreover the two last examples graphically demonstrate C–C bond formation with a C_3 structural fragment that is incorporated into the ring, which is so important in preparative work. This is just as valid for 21-10 and 21-11: The former is obtained by treating $C_{(6)}$-unsubstituted 1,3-thiazine salts with zinc; dehydrogenation of the products of 21-10 gives 21-11 which can also be obtained by other methods [310-311]. Structure 21-12 represents in general the nucleophilic addition products (at position 6, Nu = nucleophile) [301]. Thus adducts can undergo further reactions, e.g., substitution with expulsion of X, and formation of 21-11 by α-elimination of X and Nu. Numerous ring transformations proceed via ring scission to the identifiable 21-13 and 21-14 (X = SH) and recyclization (e.g., 21-15 – 21-20) (cf. [301]). Type 21-15 is a limiting case, in which formally the starting cyclic skeleton is obtained from 2-amino-1,3-thiazine-6-thiones and secondary amines (replacement of endocyclic sulfur by exocyclic "degenerate" ring transformation, cf. [59]). In all other cases endocyclic sulfur is replaced by nitrogen to form pyrimidine derivatives. Some possibilities appear in 21-16 – 21-20. The 21-21 and 21-22 diagrams show that ring transformation products can be used for other cyclizations; here, they are used for the synthesis of condensed bis-heterocyclic systems. In the case of 21-22, structure 21-6 is decomposed by solvolysis, and ultimately the previously added acylketene chloride is converted to an aminoacrylic amide in the same oxidation state (cf. [304]). Hence the reaction can be directed either back to 21-15 or 21-14, or forward after dehydrogenation to the N-monosubstituted 5-aminoisothiazoles 21-24. Structure 21-25 arises from "sulfidic constriction" of the ring, i.e., by the removal from the latter of a sulfur atom. By this transition to a pyrrole, the adduct of the C_6-unsubstituted 1,3-thiazinium salt with nucleo-

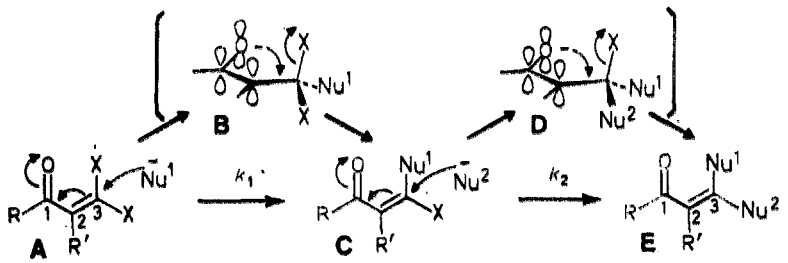


Fig. 23. Stepwise nucleophilic substitution in acylketene derivatives by a "concerted" addition–detachment mechanism; dependence of reactivity (k_1, k_2) on nucleophilic reagents Nu^1 and Nu^2, on charge stabilization of RCO and R' groups, on possible flattening of R–CO–C–R' fragment in B and D (in transitional state or intermediate), on nucleophobicity of leaving group X, on reaction medium and reaction conditions (ratio of k_1 to k_2), etc.

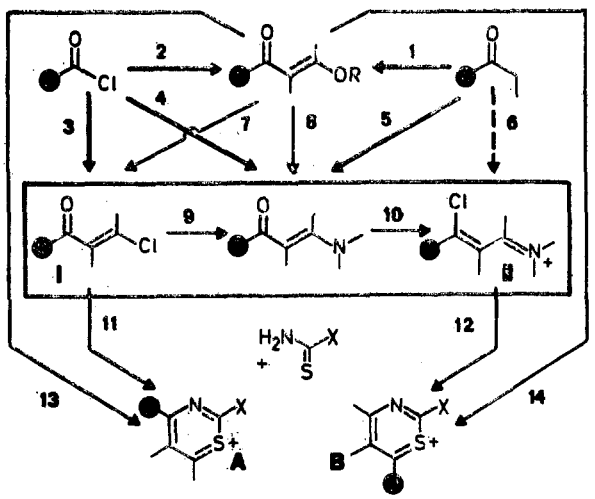


Fig. 24. Positional selectivity of reactions of C_3 components in cyclization to 1,3-thiazinium cation. Reaction routes: 1) + carboxylic ester; 2) + vinyl ether; 3) + vinyl chloride, alkyne ($AlCl_3$); 4) + enamine; 5) + amidoacetal, Vilsmaier reagent; 6) + Vilsmaier reagent [goes via (5)]; 7, 10) + chlorine source (phosgene, oxalyl chloride, thionyl chloride, Vilsmaier reagents); 8, 9) + secondary amines; 11-14) + thioamide derivatives.

phile 21-12 (X = H, Nu = NR_2, SR) is deprotonated by butyllithium; then the endocyclic sulfur is either expelled from the ring (Y = H), or in the presence of alkylating agents is converted to an alkylthio group (Y = SAlk). Here the 1,3-thiazinium cation is used in the synthesis as a latent "pyrrolium cation" [312] (cf. [157]).

2.4. Diversion: C_3-Functional Synthetic Fragments for Heterocyclization

In the overall picture of the conversions shown in Figs. 20 and 21, the 1,3-thiazine ring is a central figure in the transformations of the C_3 components. Figuratively speaking, this key role is characterized by "focusing" and "intersection" of reaction paths (cf. Section 1.3). The key role is played by the acylvinyl chlorides and acylketene dichlorides that are used for the 1,3-thiazine synthesis (Figs. 19 and 20); these form easily by various paths from C_1 and C_2-functional structural components and are converted to numerous products [242-245] (cf. also [313-316]). Among the latter the 1,3-thiazines are only a special case. These compounds are representatives of an extensive family of C_3-functional systems, which all

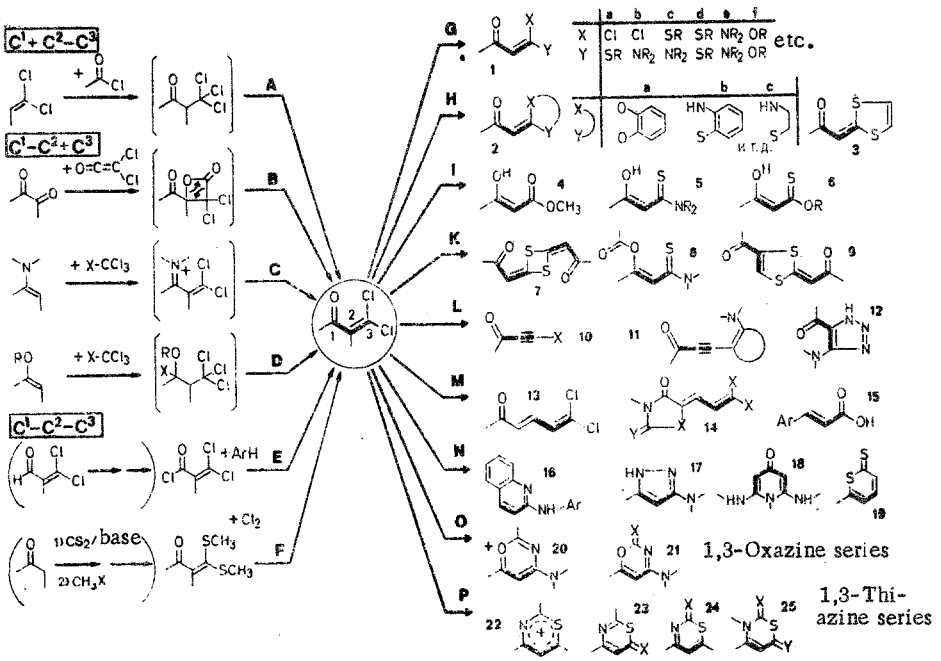


Fig. 25. Synthetic routes involving acylketene dichlorides: the key preparative role of acylketene dichlorides. It is noteworthy that in the synthesis of compound 3 vinylidene chloride performs a dual function, as both geminal and vicinal bis-acceptor ethene reagent (double substitution of chlorine in acylketene dichloride and formation of cis-1,2-dimercaptoethene necessary for cyclization according to Fig. 7).

together originate isofunctionally* from β-dicarbonyl compounds, or β-ketocarboxylic or malonic acids (more exactly, from their enol forms). They differ from these basic types only inthe kind of heterosubstituent, but the carbon function is in the same oxidation state.

These considerations are illustrated by Fig. 22. Acylvinyl chlorides [242-245] are obtained by replacing the enolic hydroxyl of β-dicarbonyl compounds by chlorine; β-chlorovinyl methyleniminium salts [313-314], by further replacement of carbonyl by iminium. Acylketene dichlorides, acylketene acetals — in short, acylketene derivatives — are "functionally equipped" carboxy enol forms of β-ketocarboxylic acids that usually do not exist because of increased energy. Since in theory these C_3-functional systems can react with nucleophilic reagents at both $C_{(1)}$ as acceptor reaction centers,† they are suitable for various heterocycle syntheses. This means that any structural fragment with 1,3-acceptor reaction centers can be built into a heterocycle. In synthesis of 1,3-thiazines from acylvinyl chlorides or acylketene dichlorides and thiocarbamoyl compounds, the C_3 functional structure fragment is introduced into the cyclic structure via nucleophilic replacement of chlorine and condensation at the carbonyl group. This principle is based on the synthesis of various heterocycles from acylvinyl chlorides and nucleophilic reagents (e.g., pyrazoles, isoxazoles, thiophenes, pyridines, pyrimidines, etc,) [242-245]. The classical example is the heterocyclization of β-dicarbonyl compounds with β-ketocarboxylic and malonic acid derivatives.

*By "isofunction" we mean all kinds of "carbon—heteroatom" bonds that have similar characteristics of polarity and heterolysis ("polarity") at the same oxidation state of the functional carbon atom (cf. the "isohypsic" concept of Henderson [78]). In theory isofunctional systems are "equipolar." By means of isofunctional conversions one can purposefully modify the reactivity of fragments, i.e., control it (cf. also the possibilities of reaction transpolarization that is important in planning syntheses, e.g., [64, 76]).

†Here we use "donor" and "acceptor" in a double sense: a) to characterize reactivity (acceptor activity = electrophilicity, donor activity = nucleophilicity, cf. [76]); b) to characterize electron effects with respect to polarity and polarizability.

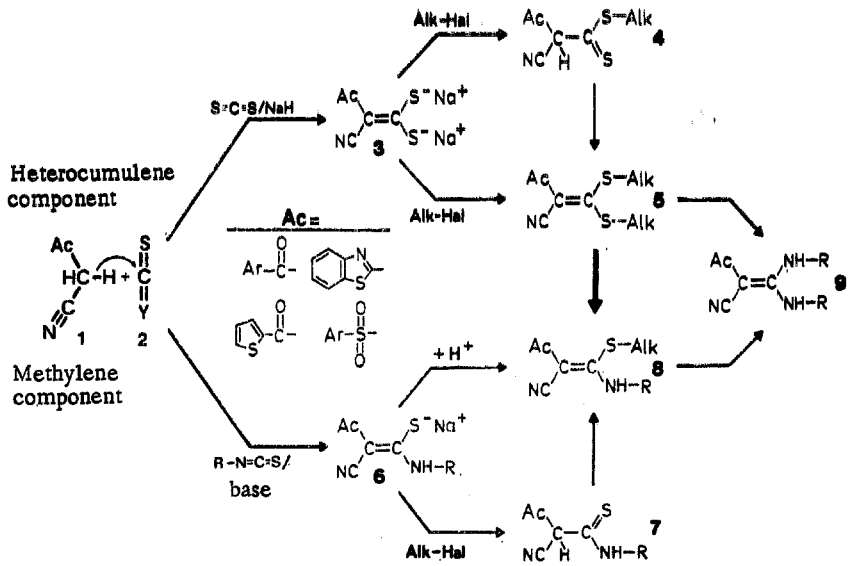


Fig. 26. Thiocarboxylation of acyl- and cyano-activated methylene compounds and the simplest subsequent conversions of the reaction products.

Nucleophilic replacement of chlorine in acylvinyl chlorides and acylketene dichlorides is also characterized by a "concerted" mechanism of $C_{(1)}/C_{(3)}$ acceptor activity of all $C_{(3)}$-functional systems; predominantly a concerted addition–detachment mechanism of the $B_{AC}2$-alkylation type [317] is realized (Fig. 23). Here acylvinyl chlorides and acylketene dichlorides can be considered as vinylogs of acid chlorides, while C_3 functional systems in general can be considered as vinylene homologs of carboxylic and carbonic acid derivatives.* The carbonyl group plays a dual role, being not only an acceptor reaction-center but also an "activator" of nucleophilic attack at position 3, in this case in the nucleophilic replacement of chlorine. This corresponds to the "acceptor-activated" vinylation of nucleophiles: acyl activated vinylation, keto vinylation, enone transfer. This principle is also extended to other acceptor carbon functions (COOR, CN, C = NR_2+, etc.) and other nucleophilic leaving groups (SR, OR, NR_2, NR_3+, CN, etc.)† This scheme also includes, as is well known, alkynes with acceptor substituents (nucleophilic addition instead of substitution, cf. Section 2.2).

In general C_3 functional structure fragments (such as β-dicarbonyl compounds and β-ketocarboxylic and malonic acids) can be called 1,3,3-triacceptor propenes, and in the ionized form 1,3-bis-acceptor allyl cations for heterocyclization (see Fig. 22; for the terminology, see [76]). The acceptor activity of positions 1 and 3 can change drastically with the nature of the heterosubstituents; this has decisive regiosynthetic consequences (orbital and charge control, cf. [115, 116, 321]). For our purposes, however, it was ultimately important that unsaturated three-carbon units with appropriate functionality could be purposefully introduced into the heterocycle; figuratively speaking, that the three-carbon blocks appropriately prepared in advance could be included in the heterocycle assembly "according to plan."

A number of examples thereof are shown in Fig. 24. The condensation of aroylvinyl chlorides with thioamide derivatives in the presence of perchloric acid gives 4-aryl-1,3-thiazinium salts (route 24-11) [296, 301, 302, 312]. But the same reaction of β-aryl-β-chlorovinylmethyleniminium salts gives 1,3-thiazinium salts arylated at position 6 (route 24-12) [322] (but see [323]). In both cases S-attack at a carbon with chlorine predominates. If we take into account that by successive aminolysis and chloridolysis aroylvinyl chlorides can be converted to β-aryl-β-chlorovinylmethyleniminium salts (routes 24-9 and 24-10, cf. also [314, 324]) then it becomes obvious that by preforming or choosing the heterosubstituents in the C_3 fragment the synthesis of 4-aryl-1,3-thiazines can finally be "developed"

*The principle of vinylology is described in a general way in [318]; cf. also [216, 242-245, 319], discussion in review [314], and further in [294, 320].

†When the leaving groups also show the π-electron donor effect (SR, OR, NR_2), one often speaks of "push-pull alkenes." cf. [294]; the double bond character of the carbon–carbon bond decreases, and a mesocarbon carbon can be used in the synthetic plan as an additional donor reaction center. For NR_3+ as nucleophilic leaving group, cf. the special review [319].

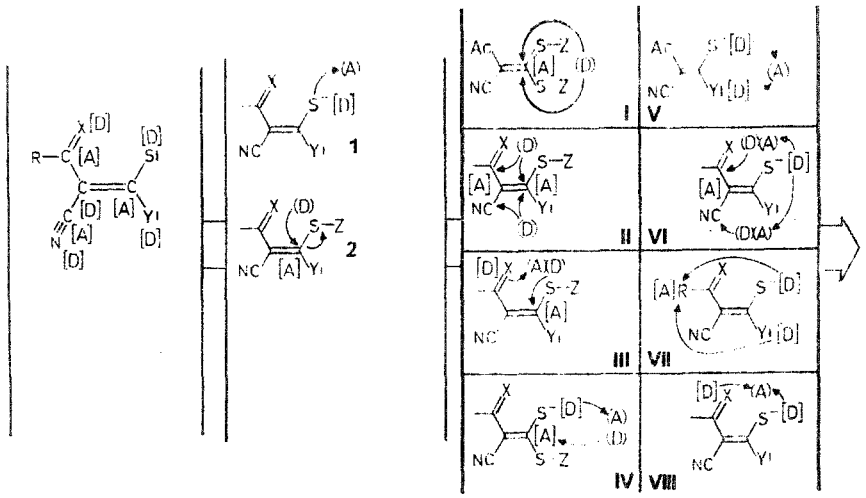


Fig. 27. Cyclizations of thiocarboxylation products obtained according to Fig. 26; cyclization types I-VIII. Reaction centers in brackets, reagents in parentheses: A) acceptor, D) donor. Fundamental reaction according to thiocumulene fragment introduced into structure: 1) with retention of S (IV-VIII), 2) with replacement of S (I-IV).

toward formation of 6-aryl-substituted products; in this way by varying the functionality of the C_3 block the 1,3-bis-acceptor reactivity can be selectively influenced. Analogously the conversion of β-dicarbonyl compounds to acylvinyl chlorides (route 24-7) [242-245, 315; 316, p. 442] is used for purposeful synthetic application. As is well known, aroylacetones react with thiocarbamoyl compounds to give mixtures of 4-aryl-6-methyl- and 6-aryl-4-methyl-1,3-thiazinium salts (routes 24-13 and 24-14) [277, 305].

Figure 25 correlates a number of synthetic routes that go via acylketene dichlorides [cf. also Figs. 19 and 20). Here also the reaction of acylketene dichlorides opens the way to numerous synthetically valuable reagents having the same oxidation state as β-ketoacids (the heteroanalog derivatives of 3-ketocarboxylic acids, acylketene (hetero)acetals, cf. especially with the data in [268, 269, 274, 275, 325-327]). Acylketene dichlorides have the advantage over other acylketene derivatives in that they take part in substitution reactions much more easily (here, the substitution of chlorine); these usually require additional acceptor activation, e.g., with the aid of a second acceptor group, or more severe reaction conditions (see the situation with acylketene mercaptals, Section 2.5). For heterocyclization one can also use dual geminal substitution of chlorine in acylketene dichlorides (as in the sulfonylketene dichlorides mentioned incidentally in [271]). In this case only one carbon of the C_3-functional structure fragment is involved in heterocyclization; i.e., the vinylidene chloride component can be considered as a 1,1-bis-acceptor ethenic reagent. Such positional selectivity is in theory shown in the behavior of all electrophilically activated ketene derivatives, including the acid-catalyzed hydrolysis of vinylidene chloride to acetic acid and the carboxymethylation of carbenium cations in strong acid medium [328]. The reaction of vinylidene chloride with mercaptans to form cis-1,2-dithioethenes, already considered in Section 2.1 (see Figs. 7, 10, 11), where vinylidene dichloride appears as a 1,2-bis-acceptor ethene, is another matter. A comparison of 1,4-dithiine and 2-acylmethylene-1,3-dithione is an excellent illustration: In the synthesis of the former, vinylidene chloride takes part twice as a 1,2-bis-acceptor ethene, whereas in the latter case it takes part once as a 1,1- and a second time as a 1,2-bis-acceptor ethene (cf. Sections 2.1.2. 2.1.3).

Finally, it is noteworthy that C_3 functional structure fragments (Fig. 19) and the 1,3-thiazinium heterocycles obtained from them (Fig. 20) are only different "storage forms" of the same three-carbon unit (Fig. 22). The 1,3-thiazines are the same isofunctional, but now cyclic, variants of the corresponding C_3 structure fragment. Strictly speaking, all heterocycles can be considered from this viewpoint, viz., how quickly they form only by the closing of a carbon–heteroatom bond. Thus, finally, the key position of 1,3-thiazines in the synthesis, which was characterised at the beginning of this section, is to be especially emphasized.

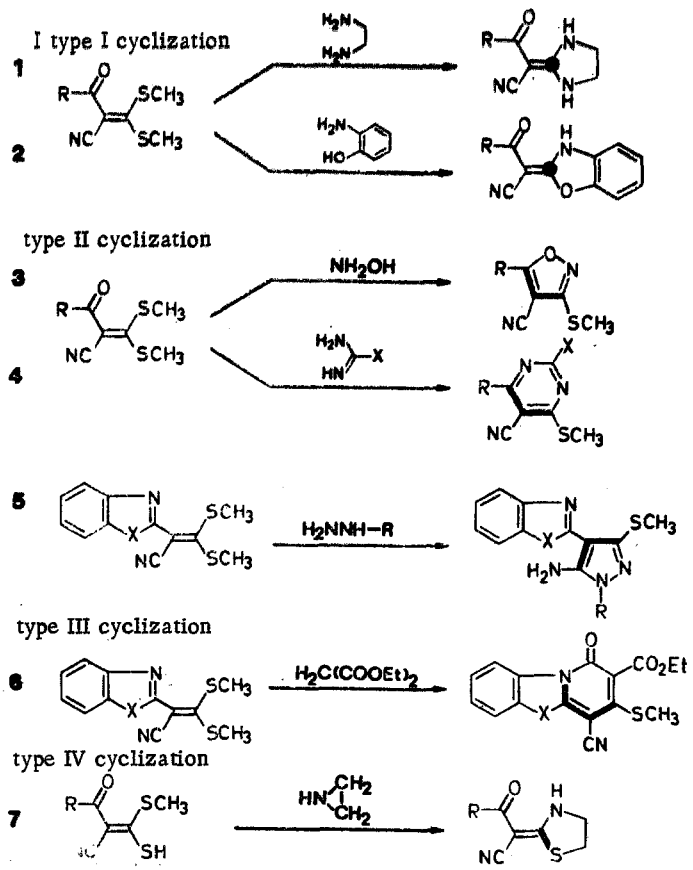


Fig. 28. Heterocyclization with participation of type I-IV cyclizations (with substitution of cycle separated by boldface line); reactions from thiocarboxylation product included in

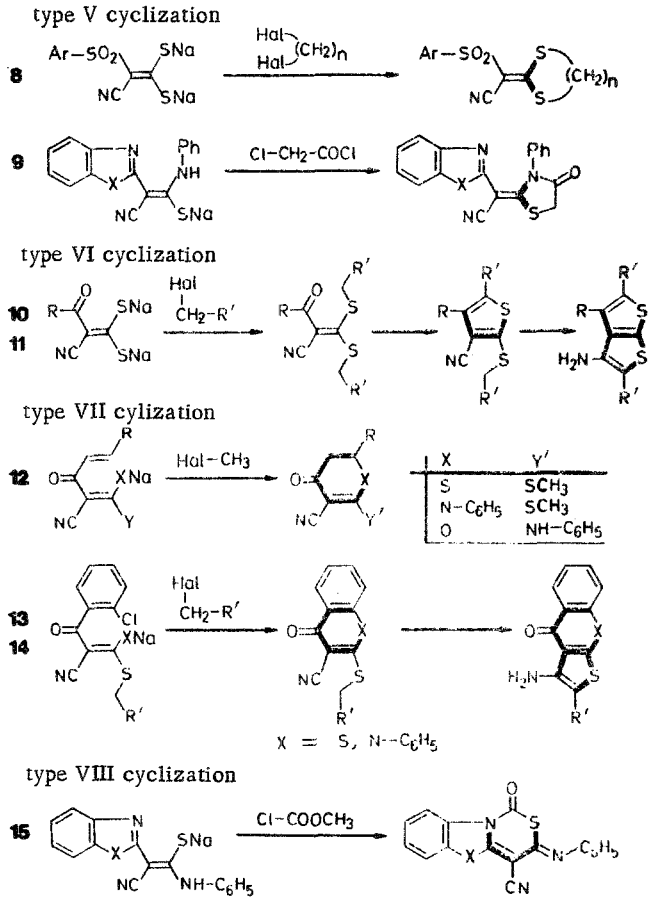
2.5. Carbon Disulfide, and Industrial Product, as a Component in Heterocycle Synthesis

2.5.1. Carbon Disulfide and Organic Sulfur Reagents

Carbon disulfide, a very important intermediate among thiocarbonic acid derivatives (for reviews see [329-331]), is important synthetically in C_1 conversions. The carbon reacts predominantly as an electrophile (acceptor activity, heterocumulative properties), while the sulfur reacts as a nucleophilic center (donor activity) [332, 333]. Hence the following varied conversions take place, even as far as the synthesis of products that do not contain sulfur. The timeliness of studies in this direction can be judged from the sudden increase in the number of articles lately devoted to organic sulfur reagents [93-95, 334-342]. It is even more remarkable that carbon disulfide has long been of fundamental importance in organic chemistry as a starting material and intermediate for the Kolbe synthesis of acetic acid (1845) [4] (cf. Part I of this review [262]).

2.5.2. Thiocarboxylation of CH Acids

The subject of this section, as shown schematically in Fig. 26, is the use of carbon disulfide (26-2, Y = S) for thiocarboxylation of active methylene compounds 21-1 (see also [343]). The products obtained by a known route (see [313-316]), especially [316, p. 409) via deprotonation of dithiocarbonate salts, or the geminal dithiolates 26-3, are alkylated to the respective dithioesters 26-4, and also to acceptor-activated ketene mercaptals 26-5 [344]. The same reaction with phenyl isothiocyanate (26-2, Y = N-C_6H_5)goes via thioanilides



thiocarboxylation products: reactions 1-7, alkylthio groups; fragments included in hetero- 8-15, type V-VIII cyclizations (heteroatom heterocycle).

26-6 or 26-7 to the respective ketene (N, S) acetals 26-8 [345]. In the most general sense we are speaking of electrophilic "heterocarboxylation" of a CH acid system by carbonic acid derivatives, in particular diheterocumulenes. For promoting the deprotonation of active methylene compounds 26-1, acylacetonitriles* are always applicable (aroyl- and heteroarylaceto- nitriles [346], arylsulfonylacetonitriles [347], azolylacetonitriles with heteroanalogous carbonyl group in the ring [348-350]). In all cases cyanoethene, i.e., the acrylonitrile structure, remains the constant molecular fragment in acceptor-activated ketene (hetero) acetals 26-5 and 26-8.

In compounds 26-5 and 26-8 one can recognize the structural principle of vinylology of derived acids (according to Fig. 23, Section 2.4). †As was to be expected, the alkylthio group can undergo nucleophilic substitution; to a small extent the cyano group strengthens

*The acceptor-activated ketene (hetero)acetals obtained from acylmethylene compounds (methyl ketones) and carbalkoxyacetonitriles (cyanacetate esters) were thoroughly studied long ago (see review [343, p. 3] and [313-316]). By using the acylacetonitriles the gap between acyl- methylene compounds and carbalkoxyacetonitriles has been filled.

†Concerning the decrease in double bond character of the carbon–carbon bond in these push-pull alkenes (see footnote on p. 1312 , the question of Z/E isomerism, and the problems of intramolecular bridged hydrogen bonds, see the detailed discussion in the review [343] and the literature cited there. The possible effect of complexation on the preferred direction of cyclization at carbonyl or nitrile groups is not always precisely predictable (See Section 2.5.3).

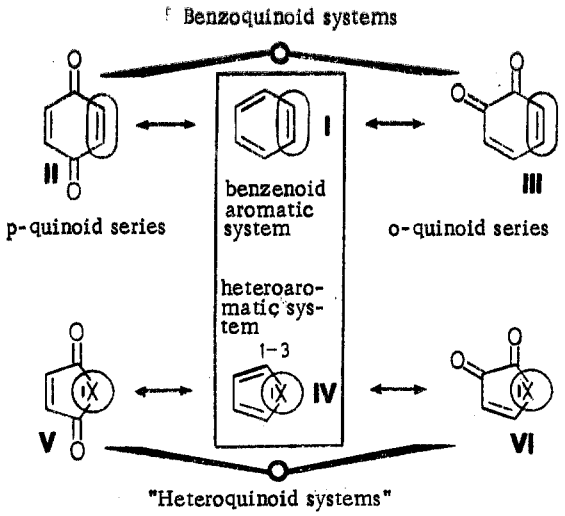


Fig. 29. Maleic anhydride, maleimide, and thiomaleic anhydride as "heteroquinoid systems" (π-isoelectronic substitution in ring). 1) X = O; 2) X = NR; 3) X = S.

the acceptor-activated structures.* A typical example of this effect is the stepwise aminolysis of 26-5 to the acylcyanoketene (N, S) acetals 26-8 and then to the acylcyanoketene aminals 26-9 [351].

2.5.3. Cyclization of Thiocarboxylation Products

The fundamental reactions at the sulfur (S-alkylation and at a carbon with a thio function (substitution of alkylthio group) demonstrate only one side of the preparatively valuable chemical properties of thiocarboxylation products. For heterocyclization there are other active centers. The extensive experimental material permits at least eight kinds of cyclization (I-VIII, Fig. 27). The heterocycles thus obtained can be purposefully modified by subsequent functionalization. The examples are as follows (besides the diagram in Fig. 27, see Eqs. 1-15 in Fig. 28).

Type 27-1 Cyclization. Under conditions for aminolysis of acylketene mercaptals to aminals, cyclic aminals are obtained if diamines are used. A representative example with geminal substitution is the reaction with ethylene diamine to give 2-methylenimidazolidines, or with o-aminophenol to give 2-methylenebenzoxazolines (Eq. 28-1 and 28-2) [351].

Type 27-II Cyclization. Heterocyclization consists of bridge formation between an acceptor-activated mercaptal carbon and the acceptor center of a carbonyl or nitrile function, using 1,2- or 1,3-dinucleophilic reagents. In the primary substitution of the alkylthio group of an acylcyanoketene (hetero)acetal by the action of hydroxylamine (Eq. 28-3) isoxazoles are formed [352]. By Eq. 28-4, reactions with amidines and carbamic acid derivatives give pyrimidines [353]. In the case of 28-5 ring closure is possible only at the nitrile group, and when hydrazines are used, pyrazoles form [348].

Type 27-III Cyclization. Substitution of an alkylthio group by the action of malonic ester gives ring closure at the nitrogen of the heterocyclic "quasi-heterocarbonyl" group. This route (Eq. 28-6) opens an approach to heterannelated pyridones [350].

Type 27-IV Cyclization. According to Eq. 28-7, the monomethyl dithioester (as the ene thiolate) reacts with aziridine to form a 2-methylene-1,3-thiazolidine ring [351]. Here heterocyclization goes via alkylation of the thiolate sulfur (aziridine scission) and nucleophilic substitution of methylthiol (by the action of the amino group).

Cyclization of 27-I – 27-IV includes substitution of alkylthio groups. But in the cyclization of 27-IV it is already possible, and in the succeeding types 27-V – 27-VIII it is efficient to broaden the synthetic possibilities of the method if the heteroatoms coming from the thiocumulene component 26-2 are present in the cyclization product as members of the ring. Cyclization is joined to the alkylation step (in this case, ring closure by alkylation, type 27-VII, Eqs. 28-12 – 28-24); here the outcome of the reaction determines the choice of alkylating agents.

*Nucliophilic replacement of SR is especially favored by the linear structure of the CN group; meantime it hardly interferes with the coplanarity of the reacting system that is necessary for acceptor activation (see also the structural diagrams in Fig. 23).

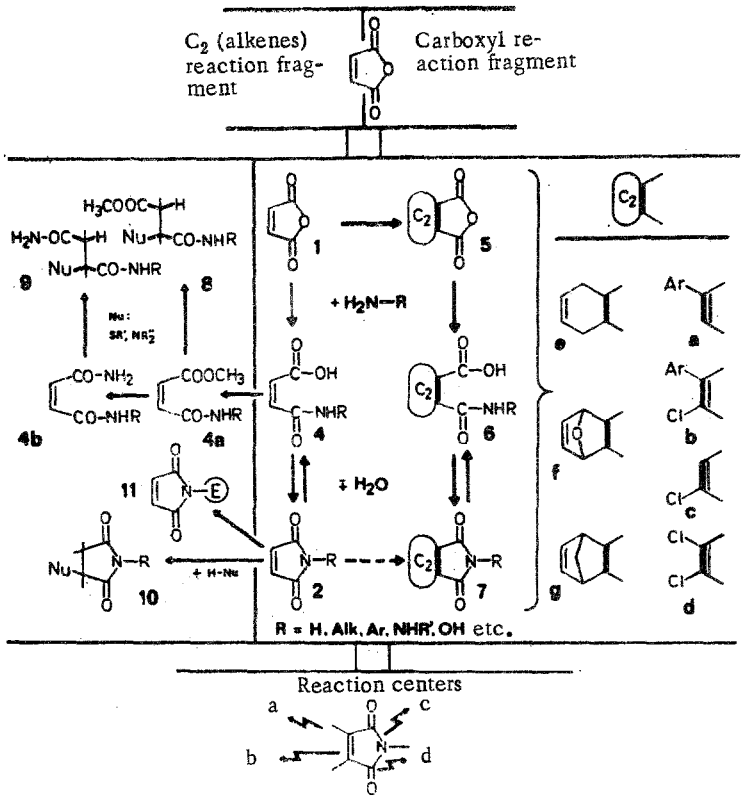


Fig. 30. Some principles of syntheses based on maleic anhydride: a) substitution b) addition c) reactions of electrophiles at nitrogen d) reactions of nucleophiles at carboxyl (condensation, scission, and ring transformation).

Type 27-V Cyclization. Here all the heteroatoms of the ketene acetal take part in heterocyclization. Reaction with dielectrophilic reagents, e.g., dihalides, gives 2-acylmethylene heterocycles with heteroatoms in positions 1 and 3 (Eqs. 28-8 [347] and 28-9 [350]). In theory the heterocycles thus obtained have the same structure as those formed by type 27-1 cyclization (Eqs. 28-1 and 28-2), but differ substantially in the origin of the heteroatoms contained in the heterocycle.

Type 27-VI Cyclization. For ring closure only one bifunctional donor–acceptor reagent is formally necessary; actually, however, the cyclization goes stepwise. From example 28-10 it is obvious that thiolate sulfur is alkylated by reagents in which the methylene group is sufficiently activated by a strong electronacceptor substituent, R' [346]. Thus ring closure can originate in the formation of a C–C bond followed by CH deprotonation. It is noteworthy that in this case nitrile is the preferred acylfunction for attack, so that the respective cyanothiophenes are formed ("Dieckman cyclization," cf. also type 27-II cyclization). The latter are capable of new cyclization, this time at the cyano group to form thieno [2,3-b]thiophenes (Eq. 28-11, "Thorpe cyclization" [354]). Analogously substituted aminothiophenes form via acylcyanoketene (N, S)acetals (derived from phenyl isothiocyanate) [345].

Type 27-VII Cyclization. The heterocyclization is based on intramolecular attack of the ketene acetal or thiocarbonyl heteroatom at a suitable acceptor center in the side chain of the alkyl group. This is typical of dithiocarboxylation, thiocarbamoylation, or carbamoylation of cinnamoylacetonitriles (Eq. 28-12) [355, 356]. After alkylation, 5,6-dihydrothiopyrane-4-ones or 4-oxo-1,4,5,6-tetrahydropyridines are obtained. We are referring ultimately to a reverse cycloaddition, within the framework of which ring transformations via N, S exchange are possible; thus, 28-13 demonstrates cyclosubstitution. Here the chlorine in the phenyl nucleus takes part in nucleophilic substitution just as in acylvinyl chloride (cf. Section 2.4, Fig. 23) [357]. This heterocyclization, which gives thiochromones and quinolones, is based on the use of O-chlorobenzoylacetonitrile and carbon disulfide or

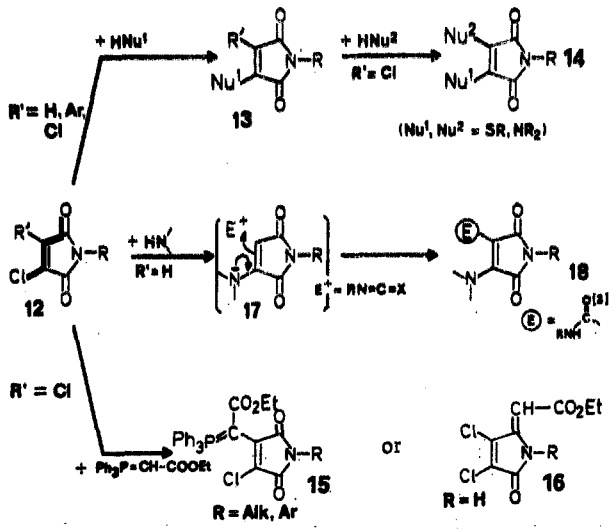


Fig. 31. Chlorine substitution in chloromaleimides (in structure 12 the acylvinyl chloride is distinguished).

phenyl isothiocyanate (under certain conditions one may use starting compounds without a CH group in the o-haloacetophenone component [358]). The reaction can proceed further according to type 27-VI (Eq. 28-14).

Type 27-VIII Cyclization: In this case (as in 27-III) a heterocarbonyl group in a ring acts as donor center. Reaction with a chloroformic ester (Eq. 29-15) gives 3-phenylimine 1,3-thiazino [4,3-b]benzimidazol-1,3-dione [350].

2.5.4. Review: Synthetic Chemistry of Products of CS_2 Reactions

We can state in conclusion: A) Type variety of syntheses is due to the variety of CH-acid reagents suitable for dithiocarboxylation (carbon disulfide) or thiocarbamoylation (phenyl isothiocyanate), the large selection of S-alkylating agents, the nucleophilic reagents for substituting alkylthio groups, and the polyfunctionality of the products of dithiocarboxylation or thiocarbamoylation (in the following reactions). B) A sulfur atom introduced into a reaction product by a thiocumulene component S=C=Y can be used in many preparative routes: in nucleophilic sulfur substitution as an alkylthio group its role remains "auxiliary," and sulfur is excluded from the further course of the synthesis (type 27-I – 27-IV cyclizations); sulfur may be included in the heterocycle that is formed, entering the final product in alkylated form (S-heterocycles; type 27-IV – 27-VIII cyclizations, Eqs. 28-I – 28-15); moreover, sulfur in the final product is ready for further conversions if it is part of an exocyclic function. C) The syntheses presented here in many ways resemble published reactions of other acylketene mercaptals or acylketene (hetero) acetals (see footnote on p. 1315). The constant presence of CN can be considered as a specific "stratagem" that enlarges the circle of applicable active methylene starting compounds (e.g., to acetonitrile) in which this group behaves both as acceptor-activating structure element and reactive functional group. Thus the supply of preparatively valuable reactions can be substantially enlarged (e.g., reactions 28-11 and 28-14).

In theory acylketene (S, S)acetals and (N, S)acetals provide many important approaches to functionally substituted heterocycles. In this connection we should recall heterocyclization with thiocarboxylation products obtained from ω-nitroaceto-phenones or β-diketones [359, 360] (for synthesis and reactions of carbocyclic acylketene (S, S) acetals see [361]). The use of (aromatic) acid amides is promising; by thiocarboxylation (thiocarbamoylation) at the amide NH_2 by the methods described above they can be converted to functionally substituted heterocycles with an additional nitrogen in the ring [362].

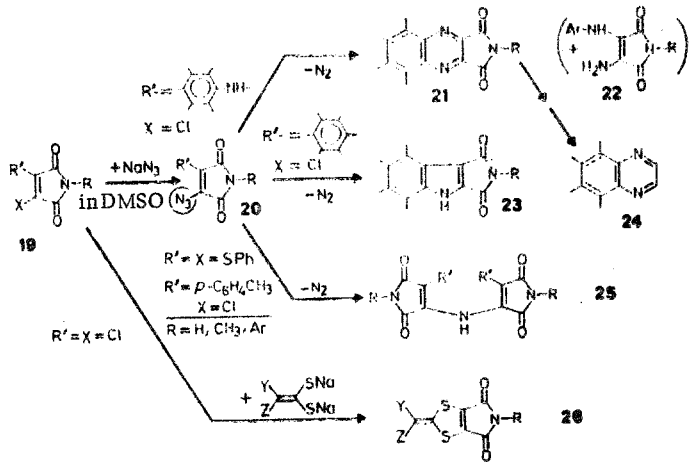


Fig. 32. Type I heterocyclization of maleimides: ring closure at alkene C_2 fragment.

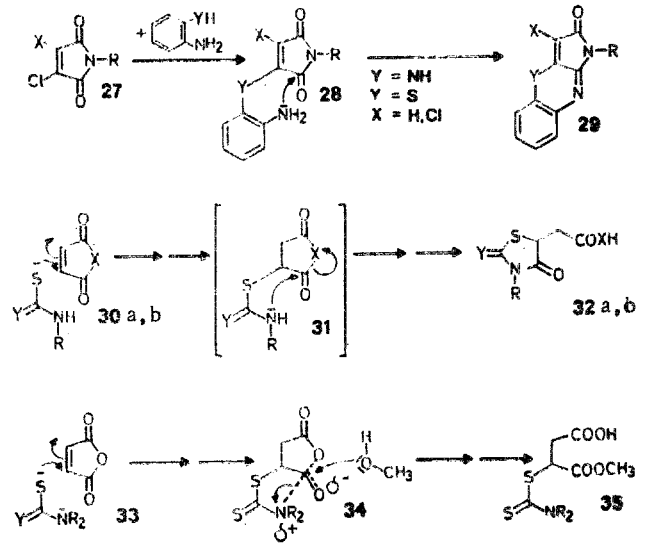


Fig. 33. Type II heterocyclization of maleic acid derivatives: ring closure with inclusion of carboxyl fragment. 32 a: Y = S, R = H, Alk, Ar, X = O, NR'; 32b: Y = NH, NAlk, NAr, R = H, X = O, NR'

2.6. Maleic Anhydride and Maleimide, Limiting Cases of Heterocyclic Structures

2.6.1. Structure Correlations

In the comparative diagram (Fig. 29), maleic anhydride (29-1), maleimide (29-2), and thiomaleic anhydride (29-3) are shown as heteroanalogs of para-benzoquinone (29-II) i.e., as quinones that are derived from five-membere heterocycles 29-IV (furan, pyrrole, thiophene). Of course they are no less derivatives of maleic acid. But the situation at the boundary between heterocyclic and aliphatic functional compounds is widely known.

Maleic acid and its various derivatives have been known for a long time; it is sufficient to recall that maleic and fumaric acids were the first examples of geometrical isomerism (postulated by van't Hoff in 1874 and confirmed experimentally by Wislicenus in 1887), and that the use of maleic anhydride made a decisive contribution to the development of extremely important cycloadditions (O. Diels, K. Alder, 1928). On the other hand, thiomaleic anhydride (29-3) has become available only recently [363, 364], which is evidence of the continuing interest in maleic acid chemistry. This interest is sustained by many important circumstances, primarily the industrial availability of maleic anhydride (by oxidation of benzene or butenes), and also its value as an industrial intermediate, e.g., its conversion to polyester resins, and not least by its polyfunctionality as C_4-structure component needed for wide synthetic applications (see also reviews [96, 365]).

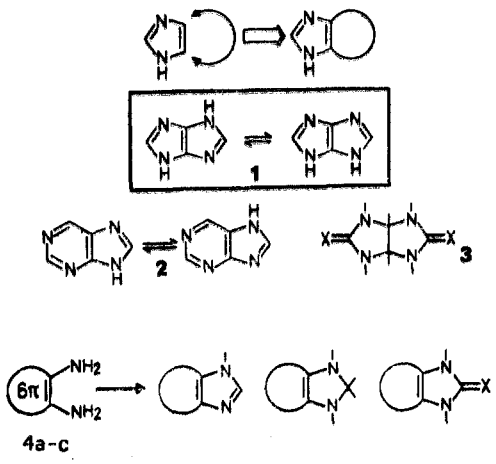


Fig. 34. Some bicyclic imidazole systems. 2) Purine series; 3) "glycol uryl" (X = O, NR), "acetylenebisurea," 4a) pyrimidine, 4b) arene, 4c) imidazole types.

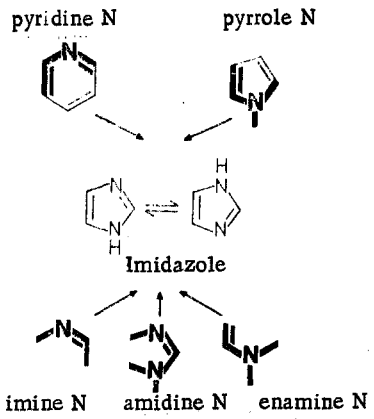


Fig. 35. Matching of N-functions with nitrogen atoms of imidazole.

2.6.2. Synthesis and Properties of Maleimides and Related Compounds

The principal theme of this section will be the chemistry of maleimide (29-2), which of all maleic acid derivatives stands closest to a heterocyclic structure (functionalization, i.e., reactions with ring retention; "pyrroloquinones;" the reciprocal influence of the carbonyl groups thanks to amide resonance). Maleimides are obtained mainly from maleic anhydride. Maleimide chemistry thus has a solid industrial foundation. Aminolysis of maleic anhydride with ammonia (urea) and primary amines gives maleic monoamides 30-4 (Fig. 30) that are easily dehydrated to maleimides 30-2 [366-370]. (Concerning aminolysis with urea, see [371], but cf. the mention in monograph [13, p. 257] of conversion to a cyclic hydrazide see [372].) On the other hand one can modify the C=C fragment at the start and obtain the substituted 30-5a-g, when then via an analogous procedure (in this case, via derivatives 30-6) is converted to the respective maleimide 30-7. Thus arylmaleic anhydrides 30-5a are obtained from 30-1 and aryldiazonium salts [373]; and the chlorosubstituted 30-5 b-d by selective chlorination. It is noreworthy that aminolysis to 30-7 can be carried out with retention of chlorine [374, 375] (cf. also the discussion below). The aminolysis components and consequently the R substitutuent in maleimides 30-2 and 30-7 can be varied widely (R = alkyl, aryl, NH-R', OH, etc.; cf. also [368]).

Addition at the C=C double bond makes possible the transition to succinic acid derivatives, whether at the stage of maleic anhydride 30-1, maleic acid monoamide 30-4 (and the derived amidoester and diamide 30-4a, b), or maleimide 30-2. In the first case we are

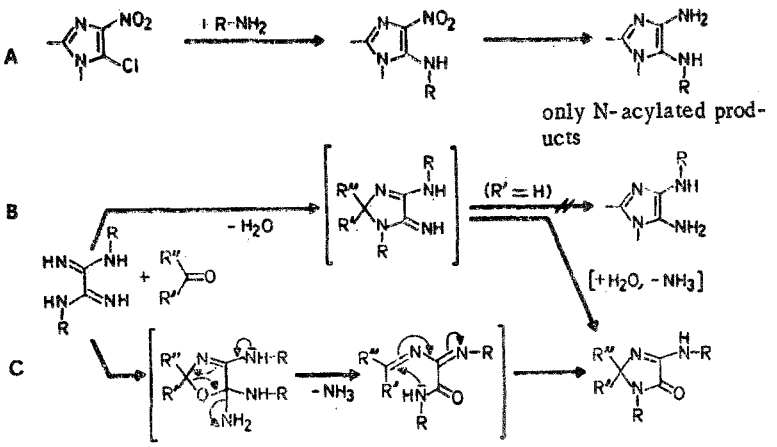


Fig. 36. Attempts to synthesize 4,5-diaminoimidazoles.

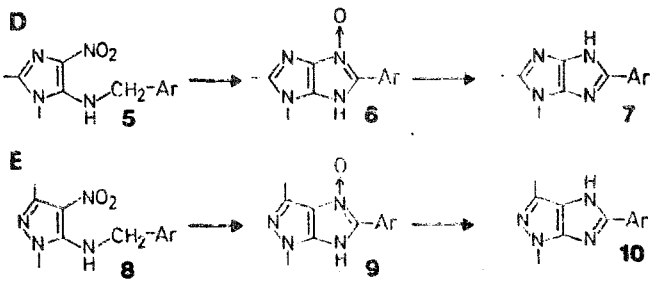


Fig. 37. Synthesis of imidazo [4,5-d]imidazoles (7) and imidazo [4,5-d]pyrazoles (10).

speaking of conversion to products of Diels–Alder cycloaddition 30-5e-g [367, 368]; in the second case, of nucleophilic addition of thiols or amines to form 30-8 and 30-9 after cis, trans-isomerization [370]. (The use of bifunctional addends such as hydrazine, ethylenediamine, or thiourea in the subsequent reaction with the carbomethoxy group of 30-4a gives heteroalicycles). In the nucelophilic addition at the C=C double bond of maleimide type compounds (as in the case described above) the electron acceptor activity of the carbonyl (enone structures) shows itself. Kinetic study of mercaptide addition to form 30-10 showed a dependence of addition rate on the nature of the R substitutent on nitrogen; thiophilicity increases with increasing acceptor influence of R [376].

Thus delocalization of the unshared electron pair of imide nitrogen (amide resonance) depends to a significant extent on the nature of the N-substituent R, the effect of which can extend to the electron interaction with aryl substituents at the C=C double bond [377]. This has been confirmed experimentally by IR, UV, and PMR spectroscopy and by polarography.

Alkaline hydrolysis of maleimides to maleic acid monoamides 30-4 is always faster than that of similarly substituted succinimides; e.g., the rate constant is 25 times larger for N-phenylmaleimide than for N-phenylsuccinimide (although from entropy considerations the hydrolysis of the latter should be favored). This rate constant decreases when a donor group (secondary amine) is located at the C=C double bond, and increases sharply when an acceptor substitutent (chlorine) is introduced. The reason for the increase in maleimide hydrolysis rate may be the increase in carbonyl reactivity due to an electron shift in the remaining enone structure fragment (hydroxyl addition as a rate-determining step) [378], but it may also lie in steric acceleration (decrease of angular strain). Hydrolytic ring scission and nucleophilic addition at the C=C double bond are most probably the decisive prerequisites of a whole series of maleimides (functional activity [379-381]. It can be presumed that the former property affects metabolism (hydrophobic–hydrophilic ratio), while the latter appears in the blocking of enzyme active centers (in the case of SH enzymes, nucleophilic addition of thiols) [382]. A typical example is the suppression of urease activity by maleimide (first mentioned in [383]); see also review [384] and the detailed summary of data in dissertation [269]).

The variety of maleimides can be enlarged even more via substitution at the imide nitrogen by the action of electrophilic reagents (according to 30-11) e.g., by alkylation, hydroxymethylation (aminomethylation), and dithiocarboxylation (using carbon disulfide). New derivatives can be also obtained from N-aminomaleimides (30-2, R = NH_2) [368]). Meantime the actual preparative value is based on reactions at the C_2 fragment, partly in combination with reactions at the carbonyl (heterocyclization), which will now be covered in more detail. One of the most important places is occupied by the chloromaleimides 30-7b-d as a starting point for synthetic conversions.

2.6.3. Chloromaleimide Reactions with Substitution of Chlorine

The approach to chlorosubstituted maleimides mentioned above (from maleic or chloromaleic anhydrides) is significantly better than the traditional approach of the reaction of chlorine with succinimide [385], thanks to the availability of the starting materials and the possibility of variation. Obviously chloromaleimides contain acylvinyl chloride as a structure fragment (β-chlorovinyl ketone; the chlorine at the C=C double bond reacts relatively easily in nucleophilic substitution, cf. Sections 2.1.5. and 2.4); the resemblance to the behavior of para-chlorobenzoquinones is also considered [386, 387].

Some preparative properties are shown in Fig. 31. The possibility of selective and stepwise nucleophilic replacement of chlorine acquired considerable significance (by routes 31-12 → 31-13 → 31-14 [388]). In 2,3-dichloromaleimides both chlorines are replaced in the reactions with amines [389], phenols [390], and thiols [391]; see also [374], where replacement of chlorine in N-arylchloromaleimides is also considered. In heterosubstitution (e.g., by the action of amine or mercaptan) the second step requires very much more severe conditions than the first step; this contrasts with the stepwise replacement of chlorine in acylketene dichlorides, the first step of which is selective only at very low temperature [cf. Sections 2.3.2, 2.4, Fig. 19 (aminolysis)]. Depending on the nature of the dichloromaleimide substitution, alkoxycarbonylmethylenephosphorane can react both with replacement of chlorine (to give 31-15) and via carbonyl condensation (to give 31-16) [392]. It is curious that aminomaleimides 31-17 with a secondary group, which are obtained from monochloromaleimides 31-12 (R' = H) and have an enamine structure, react with electrophilic reagents at the C_2 fragment, the reactivity of which is "stimulated" by enamination. Thus in reactions with isocyanates and isothiocyanates these compounds are smoothly converted to the respective carboxylic and thiocarboxylic acid derivatives 31-18 [393].

2.6.4. Heterocyclization of Maleic Anhydride and Maleimide Derivatives

Introduction of substitutuents into the C_2 fragment offers possibilities of ring closure in two ways: in the first (type I, Fig. 32) the olefin C_2 fragment can be included in the ring, leaving the carbodiimide unit intact; in the second (type II, Fig. 33) the ring can close at one of the carbonyls. To form a "cyclic bridge" in various cases only one bifunctional reaction component is enough: in the opposite case it might have to be done in a series of steps with several reagents.

Type 32-I cyclization. Here heterocyclization is characterized by ring closure with replacement of chlorine by sodium azide [394]. If an arylamino group is present as substituent (32-19, X = Cl, R' = NHAr), then detachment of nitrogen from the azide introduced in the second step (nitrene intermediate) can close the ring to form quinoxaline-2,3-dicarboximide (32-21). In the parallel reaction the azide group acts as an H-acceptor in dehydrogenation (formation of diaminomaleimide 32-22). Analogously by the action of sodium azide on arylchloromaleimide 32-19 (X = Cl, R' = Ar) via nitrene formation one can obtain the corresponding indole-2,3-dicarboximides 32-23. The same reaction with bis-phenylthio- and p-tolylchloromaleimides gives the corresponding NH-bound maleimide dimers, 32-25 (formation of deeply colored salts with alkali metals), but the mechanism of this conversion is obscure. The conversion of 5,6-benzoxinoxaline-2,3-dicarboximide to 1,4-diazaphenanthrene by the removal of functional groups (hydrolysis, thermolysis) deserves attention. This reaction emphasizes the role of the chloromaleimides as activated chloroethenes. The reaction of dichloromaleimides with ethene-1,1-dithiolate salts obtained from active methylene compounds and carbon disulfide (cf. Section 2.5) gives cyclic ketene mercaptals 32-26 (i.e., an approach to 1,3-dithiol derivatives is realized) [395]. Analogously the dichloromaleimides react with sulfhydryl transfer agents (NaSH, thiourea, etc.) to give mercaptomaleimides, which cyclize to the corresponding annelated 1,4-dithiines (cf. [385]).

Type 33-II cyclization. When chloromaleimides react with o-phenylene diamine or o-mercaptoaniline, ring closure via NH_2 condensation with carbonyl gives heteroannelated lactams 33-29 [395]. (When Y = NH the location of the double bond is controversial because here a quinoxaline structure is also possible.) Dichloromaleimides can also take part in this type of cyclization, although in theory the alternative 32-I cyclization during dual substitution of chlorine is possible here. It should be mentioned that valuable pigments have been obtained by means of these reactions [396]. The substituents necessary for heterocyclization can be introduced with the same success by nucleophilic addition at the C=C double bond; then ring closure with inclusion of the carbonyl proceeds inevitably. The reactions of maleic anhydride or maleimides with dithiocarbamates or thioureas belong to the same type of cyclization. Nucleophilic S-addition (by route 33-30 → 33-31) is followed by attack 33-31 → 33-32 at the acyl group, with "transacylation" to form rhodanine-5-acetic acids (33-32a, X = O), [269, 397, 398], rhodanine-5-acetamides (33-32a, X = NR') [369], 2-aminothiazolin-4-one-5-acetic acids (33-32b, X = O) [399], and 2-aminothiazolin-4-one-5-acetamides (33-32b, X = NR', tautomerism between 2-amino and 2-imino forms) [400]. From polarographic studies of the dependence of the rate of the reaction of maleimides (X = N-R') with monosubstituted thioureas on the nature of the substitutent on imide nitrogen it was concluded that the final step in cyclization 33-31 → 33-32 is rate-determining [400]. The most important evidence in favour of cyclization to rhodanine via formation of an N–C bond with simultaneous scission of anhydride or imide functions (and not after their solvolysis) is, in our view, the fact that the reaction of maleic anhydride with N-disubstituted (secondary) dithiocarbamates in methanol gives polyesters whose structure is certain, 33-35 [269]. In this case there is solvolytic scission of the anhydride ring that proceeds regioselectively with participation of the neighboring group to give a product that is no longer capable of heterocyclization. We should also mention the distinct biological activity of N-methylrhodanine-5-acetic acid, which is obtained from maleic anhydride and methyl dithiocarbamate (suppression of ureolysis and nitrification) [397, 398].

These examples are typical of a wide variety of applications of one of the simplest polyfunctional synthetic structure elements, represented by maleic anhydride and maleimide derivatives. All these examples have been chosen from the viewpoint of suitability for heterocycle synthesis. The rest of the field, which have been mentioned only incidentally, are applicable to such syntheses with formation of a C–C bond, which may be of preparative interest in the future.

2.7. The Imidazole Ring in Bicyclic Systems, Cyclization at a Hetarene Fragment

2.7.1. Imidazo[4,5-d]Imidazole as a Synthetic Target

In many heterocycle syntheses, ring closure takes place at an aryl nucleus to form benzene- or arene-condensed heterocycles (benzenologs or arenologs). The aryl nucleus takes the place of the C=C double bond and can affect reagent stability and reaction products, thereby facilitating heterocycle synthesis; indeed the decisive influence is often exerted by π-electron distribution and by the possibility of subsequent conversions (see also Section 2.1.4). Heterocyclizations at hetarenes ought to proceed in analogous fashion, in support of which is the structural kinship between the arene and hetarene types (see Section 1.2). These processes form "hetarenoheterocycles" or heterobicycles. The situation can be characterized as both synthesis with participation of heterocycles, and synthesis of heterocycles themsleves; one heteroring is the basis of the synthesis and the other is its target. Here are manifested two very important aspects of the synthetic chemistry of heterocycles (see Section 1.3).

At first glance the practical problem is simple: We need to obtain imidazo[4,5-d] imidazole from imidazole; in other words, to place a second imidazole ring at positions 4 and 5 of an imidazole ring (Fig. 34). (See the compendium of data on imidazo[4,5-x]-imidazole systems in dissertation [401]; see also [402]). As was recently elucidated, the fundamental heterobicyclic structure 34-1 forms in one procedure in the photolysis of 4-aminoimidazole-5-carbonitrile [403]. On the other hand, the goal can also be reached by successive stepwise synthesis, which allows for variations in starting and intermediate steps.

2.7.2 Chief Trends in Planning Syntheses

The widely known condensations to give imidazoles as well as the chemical properties of these heterocycles offer great expectations of success [404-417]. Moreover, annelation of imidazoles has been found in biologically important compounds such as derivatives of purine 34-2, an example of the synthetic art of nature. Certainly similar originals can be systematically modified by "artifical" chemical syntheses. It should be recalled that purine isomers and aza analogs have been synthesized as potential antagonists (effect on purine and nucleic acid metabolism) [418, 419]. Imidazo[4,5-d]imidazole 34-1 differs from a purine structure (imidazo[4,5-d]pyrimidine 34-2) by only one ring-carbon.

The long known reactions of α-dicarbonyl compounds with ureas and guanidines to form "glycol uryls" (34-3, "acetylene bis-ureas") clearly confirms the tendency to form the cyclic imidazo[4,5-d]imidazole σ-skeleton [401]. When we also recall that 4,5-diaminopyrimidones 34-4a or o-phenylene diamines 34-4b and carboxylic acids (or the corresponding synthetic analogs) can without trouble yield the respective annelated imidazoles (purine, guanine, xanthine, uric acid, etc. (by Traube synthesis) or benzimidazoles), then it is quite natural to choose 4,5-diaminosubstituted imidazoles 34-4c as precursor in the synthesis of imidazo [4,5-d]imidazole, by introducing it into a reaction with only one C_1 component. However it is specifically here that a problem arises.

2.7.3. Imidazole and Some Problems in Its Annelation

Imidazole includes (Fig. 35) enamine, imine, and amidine structure fragments, and has typical features of pyrrole pyridine) it is one of the most basic azoles (pK_{BH+} 7), e.g., by comparison with thiazole (pK_{BH+} 2.5), pyrazole (pK_{BH+} 2.5), and isozazole (pK_{BH+} 1.3) [13, p. 332 and following]. Thanks to the donor effect of the two amino groups at ring positions 4 and 5, its excess π-character, like its nucleophilic activity, is significantly increased. In its properties the C=C bond reached the level of an electron-rich olefin.

In no attempt at synthesis by route A (of Fig. 36) could the desired 4,5-diaminoimidazole be isolated or characterized; both amino groups are always acylated (from the nitroamine intermediate stage). Cyclodehydration with participation by carbonyl or carboxyl compounds was essentially not achieved [420]. Efforts to solve the problem by aminal condensation (possibly dual) of substituted oxamidines (e.g., "cyanoaniline") by route 36-B also did not give the desired result, but instead gave imidazolinones [401, 421]. The step at which ammonia is split out remains unclear: whether at the end of the reaction under the influence of the water formed by condensation, or according to route 36-C already at the condensation step (reaction in boiling acetic acid, nitrobenzene, or dimethylformamide).

2.7.4. Synthesis of Substituted Imidazo[4,5-d]imidazoles

Success was achievable only by bypassing the intermediate formation of 4,6-diaminoimidazole (Fig. 37). The 4-nitro-5-benzylaminoimidazoles 37-5, which are easily obtainable from 4-nitro-5-chloroimidazoles, easily undergo the cyclocondensation in methanolic sodium hydroxide that is well known for aromatic compounds. They form the light-sensitive 2-aryl-4,5-dialkylimidazo-[4,5-d]imidazole N-oxides 37-6, which are reduced by zinc dust in acetic acid to the respective substituted imidazo[4, 5-d]imidazoles 38-7 [401]. The success of the cyclization ultimately depends on various structural factors, e.g., an aryl substituent in position 2 of the bicycle, of an N-substituent in the starting imidazole. Cyclization conditions can be extended to other azole systems, as demonstrated by the pyrazole 37-8 synthesis by route 37-E [422]. The unstable bicyclic N-oxides 37-9 are converted to imidazo [4,5-d]pyrazoles 37-10 by reaction with triethyl phosphite or titanium tetrachloride at low temperature.

In addition some other principles of annelation should be mentioned (Fig. 38). Here the principal intermediates are 4-aminoimidazole-5-carbamides 38-13. Ring closure with a C_1 fragment (carboxylic or carbonic acid derivatives) corresponds to the general approach to the purine series (route 38-F). Diazotization of 38-13 always forms an intramolecular bond to give imidazo[4,5-d]-triazinones 38-14 (route 38-G). If in 38-13 the NHR is an amino-acid residue introduced at the 38-12 step, then cyclization in boiling acetic acid gives imidazo[4,5-e]diazepinediones 38-15 (route 38-H) [423]. Finally, synthetic route 38-I

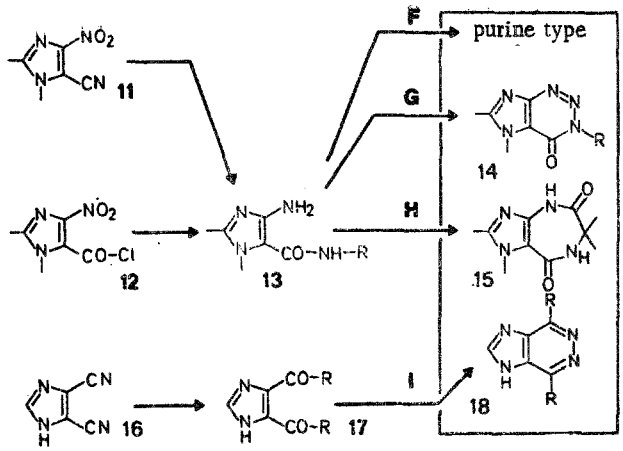
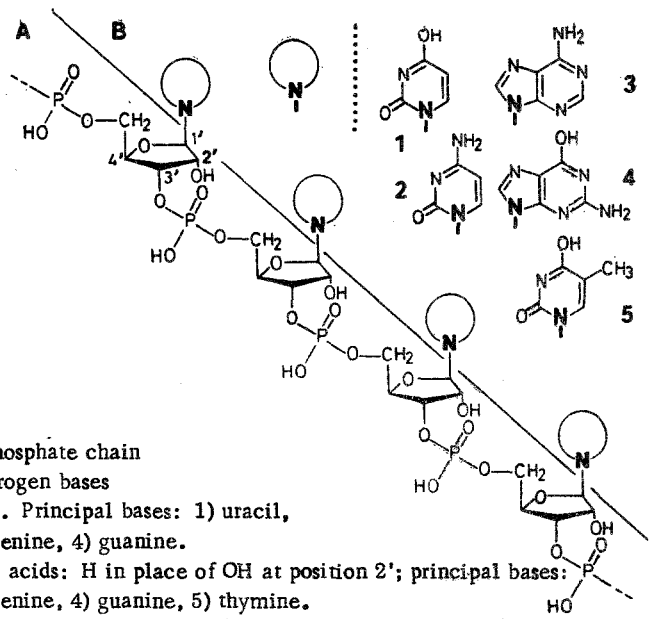


Fig. 38. Syntheses of heteroannelated imidazoles.

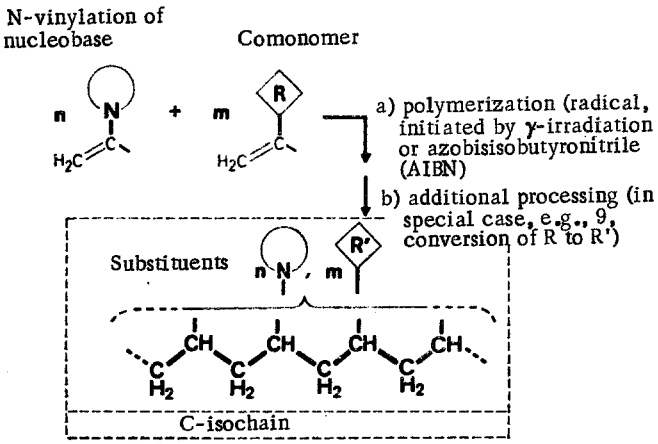


A) polypentose phosphate chain
B) "pendant" nitrogen bases
Ribonucleic acids. Principal bases: 1) uracil,
2) cytosine, 3) adenine, 4) guanine.
Deoxyribonucleic acids: H in place of OH at position 2'; principal bases:
2) cytosine, 3) adenine, 4) guanine, 5) thymine.

Fig. 39. Primary structure of nucleic acid chain (fragment).

represents a principle of annelation in which a new ring containing two carbon functional groups at positions 4 and 5 of the starting ring is built onto the imidazole ring. Here the principal starting materials are imidazole-4,5-dicarboxylic acid derivatives; the best way to prepare them is oxidation of benzimidazole with perhydrol in conc. H_2SO_4 [424]. Then the dinitriles 38-16 were obtained by the shortest route: esterification (SO_2Cl_2/alcohol), ammonolysis, and dehydration ($POCl_3$) [425, 426]. Finally, treatment of them with Grignard reagents (surprisingly simple) gave for the first time 4,5-diacylimidazoles 38-17 [426]. (4,5-Diformylimidazole 38-17, R = H, can be synthesized by MnO_2 oxidation of 4,5-bis(hydroxymethyl)imidazole [427, 428].) Heterocyclization of 38-17 with hydrazine to imidazo[4,5-d]pyridazines 38-18 thereafter is hardly trivial [426, 427]. It should be emphasized that the latter products are aza isomers of purines.

Last in order but not in importance is this circumstance: It ought to be clear from this section that in a purposeful synthesis regardless of heuristically chosen analogs and forecasts one can not only find alternative reactions that proceed unexpectedly easily, but also encounter failure. This holds even with imidazole, which is a well-known hetarene systen. In this field, as previously, there is still room for further exploration.



Bound nucleobase	Second substituent	Initiation	Monomer ratio
1) cytosine	COONa	γ	1
2) »	COONa	»	2
3) »		»	2
4) »		»	0,5
5) hypoxanthine	COONa	»	1
6) uracil	COONa	»	1,4
7) adenine	COONa	AIBN	1
8) »	SO_3Na	»	0,7
9) »	OH	»	0,7
10) »		»	0,9

Fig. 40. Products of radical copolymerization of N-vinylheterocycles (N-vinylation of nucleobases) and functionally substituted ethylene derivatives (predominantly statistical distribution and atactic configuration of subtituents in C-isochain).

2.8. Polymers from Vinylated Nucleic Bases and Analogous Vinyl Heterocycles. General Aspects of Heterocyclic Macromolecular and Biological Chemistry

2.8.1. Heterocycles in Biosynthesis as Exemplified by Nucleic Acids

In the most important biological processes heterocycles play the role of "silent partner"; heterocyclic structures determine the course of chemical reactions or affect them, often decisively, without being among the synthesis products, without visible participation in the process, and without undergoing irreversible changes. Recall the function of the imidazole ring (histidine), the thiazolium cation (thiamine) or 2-imidazolidinone (biotin) at the catalytic centers of enzymes; note the role of macroheterocyclic systems in hemin, chlorophyll, or vitamin B-12; and take as an example the basic principles of nuclei acid activity.

Nucleic acids show a new property that is unusual in "artificial" organic synthesis; the products of biosynthesis, they are capable of self-replication and act as matrices ("molecular sterotypes, patterns) for replication; indeed, their replication is required for enzyme cooperation. From our viewpoint it is most important that heterocycles give a key, so to speak, to the understanding of protein structure and the storage and transfer of hereditary information, ultimately this comes down to intermolecular reactions of nitrogen bases, complementary pairs of bases sterically distinguished by hydrogen, complementary pairs of bases sterically distinguished by hydrogen bridges, and relative orientation (due to donor–acceptor interaction) of the bases in "stacks." The latter perform the information-transfer and synthesis-regulatory functions of nucleic acids [429, 430].

2.8.2. Nucleic Acids: Structure, Functions, and Models

Figure 39 demonstrates the polynucleotide structure of nucleic acids; it shows a polypentose phosphate skeleton composed of a mixed polyester on which are "suspended" nitrogen bases isotactically to one another. From the viewpoint of heterocycle chemistry our fundamental question is: up to how much deformation, loss of identity, and modification, up to how much simplication of the polynucleotide structure, will the typical "matrix" properties introduced into the polymeric heterocycle chain be retained? [430]. Or, from another point of view: Are the intermolecular interactions of the polymer-bound nitrogen heterocycles that are especially akin to those in the nucleic acids known in principle, and to what extent are those properties comparable with those of the nitrogen bases in nucleic acids? The answer to this question might give much to the understanding of the relation between the natural structure and its properties, and might elucidate the possible control of bioregulatory mechanisms. One can at once submit a detailed listing of "imitational possibilities" that might include, e.g., synthesis of polynucleotides with changed or enlarged sequences (structural analogy), variations of carbohydrate and heterocyclic fragments (carbohydrate and base analogies), potential therapeutic value as "antimetabolites" by inclusion in metabolism [419], or a radical change of polymer matrix carrier (constructional analogy).

The following chemical synthesis [431-432] is outstanding: Models similar to native nucleic acids were synthesized by polycondensation of nucleotide residues, enzyme-catalyzed if necessary. This was achieved by first synthesizing protected oligonucleotide blocks and combining them into polymers with a regularly repeating sequence of nucleotides. From nucleoside phosphates there could be obtained both a mixed polycondensate of unknown base sequence (statistical distribution), and a homopolynucleotide with only one type of base ("synthetic polynucleotide"). The latter could already give valuable information concerning nucleic acids, especially for the development of experimental approaches to the code problem.

2.8.3. Extremely Simplified Model, Reactions of Heterocycles in Polymers

The preparative approach is drastically simplified if one completely avoids the polypentose phosphate chain as N-heterocycle carrier and uses a polymer matrix formed by ordinary polymerization of easily available monomers. In recent decades this route has aroused considerable interest not only for reproducing the way nucleic acids operate, but also for simulating the catalytic properties of proteins as "synthetic enzymes" (synzymes, enzyme modeles),for enzyme immobilization by polymer-binding, and over all for the development of polymeric catalysts [431-439]. Two routes that differ in principle lead to this goal. On the one hand, one can start from a reactive polymer chain, to which nitrogen bases are then attached by means of chemical reactions (polymer modification, e.g., reaction of appropriate N-functional heterocycles with polyvinyl alcochol). On the other hand, one uses already prepared nitrogen heterocycles capable of polymerization and attaches them by a particular technology to macromolecules (e.g., polymerization or polycondensation of vinyl heterocycles, hetaryl substituted α-amino acids, etc.). In view of the limited possibilities of the first variant (incorporation of bases into the chain), the second method is more advantageous, and is so far the most widely used for "synthesis of polynucleotide analogs" [440].

Maximal simplication is achieved by using polymers produced by vinylation of nitrogen bases (vinyl derivatives of purines and pyrimidines). "Polynucleotide analogs" are simulated by polymethylene chains with attached nitrogen bases, in other words, the functionalization of long-chain hydrocarbons, i.e., special polyvinyl derivatives. This simplication taken to its limit invloves complicated calculations and the estimation of the properties of the heterocyclic fragments; we are at the boundary of "three domains," viz., heterocyclic chemistry, the chemistry of high-molecular-weight compounds, and biochemistry.

Vinylation of nucleobases and formation of N-vinylheterocycles in general are relatively easy. The NH heterocycles are reacted with ethylene carbonate to form N-(β-hydroxyethyl) derivatives (hydroxyethylation), which are converted to the respective chloroethyl bases and then dehydrochlorinated [441, 442]. A commonly used method is vinylation of NH heterocycles with vinyl acetate in the presence of mercury (II) acetate [433, 443, 444]. Direct vinylation of NH heterocycles using acetylene [437] is among the recent methods used industrially. Often the N-vinyl group undergoes modification of other ring substituents; this circumstance has preparative value, e.g., in the conversion of 6-chloro- or 6-benzylthio-9-vinylpurine to 9-vinylhypoxanthine [442, 445].

N-vinylheterocycle polymerization is as a rule initiated by radicals, most often by using azobisisobutyronitrile [443]; γ-irradiation is widely used (low temperature, supression of competitive reactions at the heterocycle double bond). Mixed polymerization of various vinyl monomers is of decisive value; it permits polyvariant types of chains to be obtained, especially those having charge distribution and polarity closer to those found in nature, and thereby makes it possible to vary the "structure/activity" ratio [442, 446, 447]. The selection of mixed polymerizates shown in Fig. 40 indicates the great possibilities for modifying the process. Ideally these polymers are characterized by regular 1,5-bonding of nitrogen bases (corresponding to alternate copolymerization). But if the nitrogen bases are distributed isotactically, then the molecular structure becomes more favorable for pairing bases and erecting them into stacks like the natural spiral. But the practical chance of obtaining such complete regio- and stereocontrol in mixed polymerization remains doubtful, even questionable, if one starts from experience with the chemistry of high-molecular-weight compounds, even if one allows for some possible preorientation of the monomeric nitrogen bases, primarily via donor–acceptor interaction (the stacking effect) [448]. Under the conditions of radical initiation, homo- and copolymerization usually proceed "sterically at random." (According to ultracentrifuge sedimentation data, there is a relatively broad range of molecular weights with sedimentation constant S equal to 1-10, with maximum around 5-6 [447].)

Some experimental data were more unexpected, from which a conclusion could be drawn concerning definite structural uniformity, at least in some segments of synthetic polymers. Thus various poly-N-vinyl nucleobases with complementary polynucleotides form complexes with paired bases ("hybrids") that at high temperature show the hyperchromic effect that is typical of such systems [449] ("melting," i.e., collapse of the secondary structure); they definitely limit the behavior of polynucleotides [450-452]. This gives reason to consider the N-vinylated nitrogen base polymerizates as structural analogs of nucleic acids, but as very "remote" models.

2.8.4. Biomimetics of Nucleic Acid Models

The biomimetic possibilities of models extend further. Like individual nucleotides some homo- and mixed polymerizates of N-vinyl nucleobases can also be incorporated into systems of eukaryote RNA polymerases and virus revertases and show inhibitor or stimulator activity, depending on base structure and skeleton [453, 454]. Instead of polynucleotides (e.g., poly(I)/poly(C)) [455-457], vinyl polymers can also take part in interferon induction, e.g., the poly(C)/poly(vH, vCOONa) combination) [458-461]. The "antimatrix" principle [462] that is increasingly important for developing bioeffects involves the ability to compete, viz., with polynucleotides (nucleic acids, the matrixes) for a biogenic substrate (e.g., an enzyme). Finally there are comparable biological effects based on the cooperativity of low-molecular-weight compounds with the nitrogen bases of nucleic acids, e.g., intercalation (penetration) of perflavins and their derivatives (acridines), actinomycin (antibiotic activity), and thylorone (interferon induction via fluorenone derivatives) [461, 463-466]. The range of possibilities is broad and tempting for theoretical discussions, but the starting point remains the specific reactions of heterocyclic systems.

3. PROSPECTS

"Hypotheses are the scaffold that is erected around a building and is removed when the building is ready. They are necessary to the worker, but one must not take the scaffold for the building" [467].

The researcher of heterocycle chemistry understands these words well, because the value and originality of an edifice often require extremely bold auxiliary structures; their worth lies in their expediency, but the danger is that they may become ends in themselves. The countless possibilities of going along a "comfortable" route of functionalization and derivatization broaden the research effort, but depending on application, they leave no room for innovation.

And although the "systematic decoration" of heterocycle chemistry remains a permanent problem, innovative achievements are undoubtedly penetrating it from the outside: Heterocycle chemistry is alive and developing, thanks to its interaction with other branches and problem areas of science. The importance of the unexpected contribution quite recently

of complex catalysis through its approach to pyridine derivatives via the cyclotrimerization of acetylene with nitriles [468] can be estimated from the previous roundabout synthetic paths. To what extent have coordination chemistry and sterochemistry boosted the development of the synthesis of macrocyclic systems and intermediate size heterocycles (crown ethers, cryptants)? How tightly interwoven are heterocyclic, coordination, and heteroorganic chemistry (metallocycles)?

But, on the other hand, the problems of heterocyclic chemistry can exert a decisive influence. Did not the multistage synthesis of vitamin B-12, a subject of heterocyclic chemistry, one of the most brilliant recent achievements of the synthetic art, contribute *en passant* a basic scientific conclusion concerning the retention of orbital symmetry in synchronous processes [66, 117, 118, 469]?

As before, on the agenda are the construction problems of organic chemistry, the development of organic synthesis, and ultimately the rational planning of organic experiments, or, as aptly named in the English-speaking countries, "the design of organic syntheses." At the beginning of organic chemistry stood synthesis; synthesis was essential (Wöhler, 1828; Kolbe, 1845). Synthesis in its broadest sense will from now on ensure the independence of organic chemistry: "In a sense organic chemistry is a language in which substances are words, reactions are the grammer, reacting compounds are phrases, and syntheses are the sentences. Obviously the solution of synthetic problems relies directly on knowledge of structure and reactions, exactly as a sentence depends on words and grammar. It is just as obvious that dexterity comes with practice and experiment, and this is just as valid for organic chemistry as for any other language" [57, p. 908].

One more very important prospect of its future direction: Whenever the problem of systematizing and evaluating the rapidly increasing flow of information for overall forecasting arises, it becomes necessary to introduce this information into a training program. When this happens, not only has research fostered training, but training has helped research: In its many-sided interrelationship heterocycle chemistry will be a fertile field not only for scientific research but also for training, for scientific exploration as a training tool. The attributes of youth — imagination* and thirst for adventure — are also just as necessary as the "virtues" of accurate observation† and critical thinking.

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*J. van't Hoff delivered an introductory lecture on the subject of "Imagination in Science" at the University of Amsterdam on October 11, 1877 ([470]).

†It is noteworthy that one of the grand masters of organic chemistry, E. Fischer (1852-1919), spoke preferably not of researchers but almost always of observers; in his Nobel Award address in 1902 he predicted that the future progress of science primarily would be "due to the systematic collaboration of many observers." In the instructions that he regularly distributed to his trainees, the following appears: "You are urgently warned, in observing phenomena and performing analyses and other measurements in whatever manner, not to affect them by the use of theory or other preconceptions" (see [471-473]). Even earlier his teacher A. von Bayer (1835-1917) wrote: "What distinguishes the present-day investigator of nature? He should not dominate, but listen; he should accommodate himself to what is perceived and refashion himself" (cited in [474, p. 132]). We should also recall the words of G. Wald in his Noble Award address in 1967: "An experiment is a ruse by means of which nature is forced to speak understandably. After that one need only listen" [475].

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