Elucidation of mechanisms and discovery of novel reactions are interconnected, as four research chapters from the Munich laboratory demonstrate. 1) In a new opening of the furan ring, 2-methoxyfuran and tetracyanoethylene furnish methyl acrylates, which are cis-3-substituted by a cyclopropyl ring that bears the four acceptor groups. Experiments with trans- and cis-1,2-bis(trifluoromethyl)-1,2-dicyanoethylenes (BTE) clarify the role of zwitterionic intermediates. 2) The concerted nature of 1,3-dipolar cycloaddition is well established. On reacting thiocarbonyl S-ylides as electron-rich 1,3-dipoles with tetracyanoethylene-substituted ethylenes, the switching to a two-step pathway via zwitterion was diagnosed from a loss of stereospecificity and the formation of strained 7-membered cyclic ketene imines. 3) Stable as crystals, these ketene imines rearrange to 5-membered thiolanes in solution. In contrast to open-chain ketene imines, the cyclic representatives add vinyl ether at the C=N bond and show a novel pathway of dimerization. 4) Cycloadducts of isoquinolinium N-phenylimide with ethylenic dipolarophiles undergo an acid-catalyzed [3.3] sigmatropic hydrazo rearrangement. An exception is the conversion of the dimethyl maleate adduct (C_{21}H_{20}N_{2}O_{4}) by acid into a yellow compound C_{16}H_{12}N_{2}O_{6}; the structure and the astounding mechanism were clarified.

Key words rearrangement; cycloaddition; furan ring-opening; cyclic ketene imine; zwitterionic intermediate; 1,2-dihydroisoquinoline derivative

1. Introduction

Two hundred years ago, the chemical science was an undisvided field; around 1900 a division into inorganic, organic, and physical chemistry became necessary. The increase of factual material enforced a progressive segmentation into subdisciplines. A map shows countries and regions neatly separated; similarly, the uninformed observer may regard chemistry as a side-by-side of numerous disciplines and specialties. The comparison is fallacious, however, because broad overlap is thwarting clear divisions.

Heterocyclic chemistry offers an example for the lack of distinct demarcations; in fact, it pervades the plurality of the other chemical disciplines. Heterocycles are inextricably woven into the life processes. Nucleic acids, carbohydrates, macroyclic dyes, coenzymes, and alkaloids may be quoted. The vital interest of the pharmaceutical and agrochemical industries in heterocycles is often connected with their natural occurrence. Synthetic chemistry provides a cornucopia of applications with the carbanionic charge is transferred to the cyano groups. The key step of the novel conversion is an intramolecular nucleophilic substitution with the carboxyl ester as leaving group. It is one and the same reaction step, which is responsible for the closure of the three-membered ring and the cleavage of the furan ring.

Nothing is without precedent. In 1986, Ibata and associates reacted 5-alkoxoxyazoles with TCNE. The initial electrophilic attack gave likewise a zwitterion and the ring opening provided the methyl ester group (Chart 1).

How does the opening of the furan ring come about? Electrophilic attack by TCNE at the nucleophilic 5-position gives rise to a zwitterion. The cationic portion is a carboxylic ion, whereas much of the carbanionic charge is transferred to the cyano groups. The key step of the novel conversion is an intramolecular nucleophilic substitution with the carboxylic ester as leaving group. It is one and the same reaction step, which is responsible for the closure of the three-membered ring and the cleavage of the furan ring.

Deeper insight was expected from applying a trans,cis pair of tetra-acceptor-substituted ethylenes as a stereochemical...
probe. In the last decade, we repeatedly made use of the 1,2-
bis(trifluoromethyl)-1,2-dicyanoethylenes (BTE) (Chart 2),
which were first described by Proskow, Simmons, and
Cairns.4) Trans and cis-BTE, as the long name is abbrevi-
ated, boil at ca. 100 °C and can be stored in the refrigerator.
The disadvantage of an inconvenient access is more than
made up for by the superb product analysis with fluorine
NMR. Nucleophilic catalysts equilibrate the geometrical iso-
mers to a 95 : 5 mixture.

Trans-BTE is less reactive than TCNE. In contact with 2-
methoxyfuran, the orange charge-transfer color faded in 5 h.
Fluorine NMR analysis revealed the quantitative formation
of diastereoisomeric methyl acrylates, which contain
trans- or cis-located CF3 groups in the cyclopropane ring.5) The two
1 : 1 products were separated, and the combination of proton
and fluorine NMR parameters allowed an elegant structural
assignment (Chart 2). The trans form is chiral, whereas the
cis isomer has a plane of symmetry. The reaction was studied
by my associates Urrutia-Desmaison and Mloston.

When the reaction was monitored by fluorine NMR, it
turned out that equilibration of trans- and cis-BTE was faster
than product formation. The donor furan is an efficient cata-
lyst for this equilibration. A simple explanation consists in
the formation of the zwitterion, rotation about the marked
bond and reversal to the ethylenic reactants (Chart 3).

In the reaction with 2-methoxyfuran, trans- and cis-BTE
afforded the same trans/cis ratio of the two 1 : 1 products,
within the analytical limits. That means, the intramolecular
substitution takes place from an established rotational equi-
librium of the two zwitterionic conformations, trans and cis.
Thus, the intermediate zwitterion rests in a trough of the en-
gy profile and can do three things: rotation, dissociation,
and furan ring cleavage. There is even a fourth reaction:
Mloston observed a rapid equilibration of the zwitterion with
(2+2) cycloadducts (four with trans-CF3, one with cis-CF3
groups)6) that will not be discussed here.

Time-dependent concentration measurements by 19F-NMR
provided the rate constants for the ring opening of donor fu-
rans with BTE. 2-Methoxyfuran is more nucleophilic than 2-
p-tolyloxyfuran, as reflected by an 87 times higher rate con-
stant k2 (Chart 4).

The zwitterion has a higher polarity than the reactants; due
to enhanced solvation, its equilibrium concentration should
be greater in polar solvents than in nonpolar ones. For 2-p-
tolyloxyfuran, k2 is in nitromethane 1200 times faster than in
benzene. That leaves no doubt that k_i/k_{i+1}, i.e., the equilibrium
constant of the zwitterion, increases with solvent polarity.5)

When the donor furan reacted with BTE in the presence of
0.5 M pyridine, the furan aromaticity was restored. The pro-
ton in position 5 of the zwitterion is picked up by the base
and delivered at the carbanionic center. The ring cleavage of

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Born 1920 in Gerolstein, Eifel (Germany), Rolf Huisgen studied chemistry at Bonn
and München. In 1943 he obtained the Ph. D. at the University of München; his the-
sis, directed by Heinrich Wieland, dealt with strychnine alkaloids. Huisgen served as
assoc. prof. at the University of Tübingen, 1949—1952, and as full prof. at the Uni-

Rolf Huisgen’s research activity (>550 publications) concerned topics of physical
organic chemistry, reaction mechanisms, and cycloadditions.

Huisgen obtained many awards, e.g., the Roger Adams Award of the Am. Chem.
Soc. (1975) and the Otto Hahn Prize in Chemistry and Physics from the German
Chem. Soc. and the German Phys. Soc. (1979); he received honorary Ph. D. degrees
from six universities. Rolf Huisgen is member of many academies, among them the
Nat. Acad. Sci., Washington (1989), and honorary member of many learned societies,
e.g., the Royal Soc. Chem., London (1981) and the Pharmaceutical Society of Japan
(1985).
the furan was suppressed in favor of the substitution product which occurs in threo and erythro configuration. The NMR spectra disclose 2,5-disubstituted furans with the \( \beta \)-H hydrogen-bonded to the oxygen (Chart 5).5)

Dimethyl 2,3-dicyanofumarate and dimethyl 2,3-dicyanomaleate constitute a second trans, cis pair of tetra-acceptor-substituted ethylenes which opened the ring of donor furans. The trans, cis equilibration (87:13), catalyzed by the nucleophilic furan derivative, was likewise fast; the zwitterion entered into substitution and ring opening in parallel reactions.7)

3. 1,3-Dipolar Cycloadditions: Switching from Concerted to Two-Step Pathway

Concerted or stepwise is a central question of cycloaddition chemistry. All evidence for concertedness is indirect. Every single criterion may be countered with objections. In contrast, the dip in the energy profile, due to the occurrence of an intermediate in a two-step reaction, invites to interference. As a mechanistic criterion, the capturing of an intermediate has the power of conviction.

The term concerted defines the simultaneous formation of the two new \( \sigma \)-bonds in a cycloaddition. Synchronous is the rare case of equal strength of the incipient bonds in the transition state; it is more or less limited to symmetrical systems like butadiene + ethylene. Bond formation in concert embraces all cases of unequal development of the new bonds in the transition state.

In the language of the MO theory, two \( \pi \)-HOMO–LUMO interactions are responsible for establishing the two new \( \sigma \)-bonds. A limiting case is foreseen when one HO–LU interaction strongly dominates and the second becomes negligibly small. That means: The second HO–LU pair contributes so little bond energy to the transition state, that it cannot out weigh the higher entropy requirements of the concerted process. A unilateral electron flow should establish one bond between the reactants; a zwitterionic intermediate would be generated.8)

We searched for such a switch from the concerted to the two-step mechanism among 1,3-dipolar cycloadditions. It turned out that a second condition has also to be fulfilled: Strong steric hindrance at one terminus of the 1,3-dipole.

1,3-Dipoles are allyl anions with an onium function as middle center. Since sulfur has the same electronegativity as carbon, thiocarbonyl ylides should have high \( \pi \)-MO energies, approaching those of the allyl anion itself. The MO energies of acceptor-substituted ethylenes are low. The consequence is one large and one small HO–LU interaction.

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Thioketones and diazomethane furnish 2,5-dihydro-1,3,4-thiadiazoles, as exemplified in Chart 6 for 3-thioxo-2,2,4,4-tetramethylcyclobutanone. Such thiadiazolines eliminate \( \mathrm{N_2} \) and provide thiocarbonyl ylides. These highly reactive 1,3-dipoles are not isolable, but easily interceptible by suitable dipolarophiles9); thiolanes are formed with C=C double bonds. The tetramethylcyclobutanone system is an accidental choice. Other thiocarbonyl ylides react similarly.

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The addition with dimethyl fumarate proceeded with retention of the trans configuration; the cis spiroadduct remained below the analytical limit of 0.03%, as observed by Langhals. Thus, the stereospecificity amounts to > 99.9%.10)

Cis disubstituted ethylenes are less active dipolarophiles than the trans isomers. The capturing of the 1,3-dipole with maleonitrile was incomplete, and 11% of the thiocarbonyl ylide entered into electrocyclization, providing the thirane.
Nevertheless, the stereospecificity of thiolane formation still amounted to 99.9%, well in accordance with concertedness.

Mloston and Langhals observed a violation of the retention principle for the reaction of our thiocarbonyl ylide with dimethyl dicyanofumarate and dicyanomaleate. Four acceptor substituents lower the \( \pi \)-MO energies. Ratios of \( \text{trans} \) and \( \text{cis} \) spirothiolanes of 61 : 39 and 25 : 75 were observed (Chart 7). Under the reaction conditions, hardly any isomerization of the excess of dipolarophile was noticed. Rotation in a zwitterionic intermediate is responsible for the loss of stereoscopic integrity. The two-step pathway has been reached, and one bond is established here between the two reactants.10)

It is worth mentioning, that the borderline case of a two-step mechanism has also been reported by Quast \textit{et al.} for the reaction of an electron-deficient 1,3-dipole with an electron-rich dipolarophile.11)

An extreme, \textit{i.e.}, a complete equilibration of \( \text{trans} \) and \( \text{cis} \) zwitterion, was attained with 1,1,3,3-tetramethylindane-2-thione S-methylide as a 1,3-dipole. The additions with dimethyl dicyanofumarate or dicyanomaleate furnished one and the same 8 : 92 thiolane mixture without preceding dipolarophile isomerization, as found by Giera (Chart 7).12)

Oddly enough, it is the \( \text{cis} \) compound, which is preferred; the X-ray structures of both adducts, carried out by Polborn, left no doubt.

The reaction of the thiocarbonyl ylide of the tetramethylcyclobutane series with tetracyanoethylene in absolute tetrahydrofuran at 45 °C provided 84% of the cycloadduct, the tetracyanospirothiolane. Nobody would suspect any complication. However, a reaction drama was brought to light, when Mloston repeated the experiment in tetrahydrofuran (THF) that contained 1.2% of methanol. The yield of the thiolane sank to 33%, and 64% of a crystalline compound was isolated which contains an additional molecule of methanol. It turned out to be the 7-membered lactim ether, an \( S,N \)-acetal (Chart 8).13) The spirothiolane of the upper line is stable to refluxing methanol and cannot occur on the pathway to the 7-membered ring.

Two intermediates are assumed in the reaction course. In the carbanionic portion of the zwitterion, the negative charge is distributed by resonance over carbon and nitrogen atom. Competing with the 1,5-cyclization is a 1,7 ring closure, in which the terminal nitrogen slips into the electron gap of the carbosulfonium ion. The product is a strained cyclic ketene imine that adds methanol to give the lactim ether.

The cyclic ketene imine must be connected with the zwitterion by an equilibrium. Otherwise, the high yield of the thiolane in the absence of methanol could not be explained. Is this a wild speculation?

Not so. BTE has been mentioned above. Its interaction with the thiocarbonyl ylide gave rise to two products in 84 : 16 ratio. The major compound, pale-yellow crystals, is in fact the cyclic ketene imine, and the colorless minor product is the thiolane (Chart 9). The ketene imine reacts with methanol affording the lactim ether, and with water the spiro lactam. Oshima succeeded first in isolating the ketene imine in our laboratory.14)

What makes the 7-membered cyclic ketene imine remarkable? The cumulated system creates high strain in a 7-membered ring. Allene type bond systems want to be linear. Here it must be twisted and deflected to fit into a 7-membered ring.
Only few compounds with cumulated double bonds in an 8-membered ring have been isolated (Chart 10). A dibenzylketene imine was described as an unstable oil which could not be obtained analytically pure. The carbodiimide, prepared from pentamethylenethiourea, gave correct analyses, but slowly oligomerized. The tert-butyl group appears to protect the 8-membered cyclic allene, which was spectroscopically characterized.

Our ketene imine is the first stable cumulene embedded into a 7-membered ring. The stabilization comes from the perfluoroalkyl effect. Strained rings gain kinetic stability and become isolable when they contain a sufficient number of CF₃ groups (Chart 10). Hexakis(trifluoromethyl)benzvalene exceeds the parent substance in stability.

In splendid work, Dewar-pyrroles, Dewar-furan, and thiophene were prepared by Kobayashi. The origin of the trifluoromethyl effect is still unclear.

4. The Chemistry of Strained Seven-Membered Cyclic Ketene Imines

Besides the ketene imine with the tetramethylcyclobutanone ring, the interaction of BTE with three more thiocarbonyl ylides furnished crystalline ketene imines (Chart 11). They are storable in the deep-freeze under argon; quick handling in the open air causes no losses. The cyclic ketene imines show the strong IR absorption of cumulated systems. Two X-ray analyses confirmed the structures, and that of the ketene imine with the tetramethylindane residue is illustrated. The bond lengths of the ketene imine group are rather normal, but the angles are strongly deformed. The linear system of open-chain ketene imines has shrunk from 180° to 163°.

How does the strain influence the reactivity of the cyclic ketene imine?

The ring strain is responsible for the slow isomerization to the thiolanes in solution. Compared with the short-lived ketene imine which occurs in the TCNE reaction of Chart 8, a kind of slow-motion picture is watched here (Chart 12). According to measurements by Langhals, the rate of isomerization follows the first order. The half-life at 60 °C amounts to 100 h in cyclohexane and to 7 min in the highly polar acetonitrile. The rate increase by three powers of ten indicates an enhancement of charge separation in the transition state; that is in harmony with the intermediacy of the open-chain zwitterion in this rearrangement.

Despite the steric hindrance by four methyl groups, the cyclic ketene imines react rapidly with diazomethane. The spiroindane compound on the first line of Chart 13 added the 1,3-dipole at the C₅N double bond and afforded the triazole derivative in 80% yield. An X-ray analysis revealed the structure with the difluoromethylene group. Formally, the initial 1,3-cycloadduct has lost hydrogen fluoride, but the sequence of steps may be more complex.

Amusingly, the corresponding triazole was only a minor product in the reaction of the ketene imine, which is spiroannulated with the tetramethylcyclobutanone. The major product was the iminocyclopropane, the formal CH₂-adduct at the C=CC double bond. Giera noticed that this is not the
final product; a chelotropic elimination leads to the ring-opened isonitrile.12) Cyclopropanimines without the tether of an additional ring have been described; they undergo the cleavage to olefin and isonitrile at 150 °C.25) In our example, the release of ring strain promotes the reaction.

Normal open-chain ketene imines do not react with vinyl ethers. Ring strain and CF3-substitution accelerate the (2+2) cycloaddition of our cyclic ketene imines with ethyl vinyl ether (Chart 13).13C-NMR and an X-ray analysis established the addition to the C=N double bond, probably in a two-step process.12)

The propensity of ketenes to dimerize is not shared by open-chain ketene imines. However, the cyclic ketene imine of the spiro-indane series was converted to a dimer by nucleophilic catalysis (Chart 14), as observed by Langhals.26) A few crystals of potassium cyanide in acetonitrile induced a rapid dimerization that furnished two diastereoisomers in 1:1 ratio, both crystalline. The X-ray diffraction brought to light an unusual structure that is not related to the two well-known types of ketene dimerization. Thus, relief of ring strain appears to be again the driving force.

A plausible, but speculative, pathway is formulated in Chart 14 for the fluoride anion as chain-transfer agent. The primarily generated allylic anion flips the ring open. The thiolate generated attacks a second molecule of ketene imine. The new cyclic anion transfers a fluoride ion, which initiates the next reaction cycle.

5. Astounding Reactivity of a 2-Amino-1,2-dihydroisoquinoline Derivative

Isoquinolines belong to the best studied heterocycles. Nevertheless, surprises do occur. Isoquinolinium N-phenylimide shows the bond system C=N+= N−, which characterizes an azomethine imine in the classification of 1,3-dipoles.27) The colorless solution of N-anilinoisoquinolinium chloride became deep-red when triethylamine was added. The N-phenylimide was not isolable, but easily reacted in situ with dipolarophiles. A neutral source of the 1,3-dipole was offered by the crystalline adduct of carbon disulfide. Its red color in organic solvents indicated a dissociation equilibrium that is rapidly established (Chart 15).28,29)

The red color disappeared on addition of dimethyl fumarate, and two diastereoisomeric trans-diesters were formed.28,30) The retention of dipolarophile structure is a criterion of concertedness. The adducts are derivatives of phenylhydrazine in which the β-nitrogen bears an ethylenic system. Such compounds are amenable to Fischer’s indole synthesis.

This textbook procedure was discovered in 1883.31) In acidic media, ketone phenylhydrazones are converted to substituted indoles. The mechanistic scheme was devised by Robinson and Robinson in 1918 (Chart 16).32)

The phenylhydrazone is equilibrated with the vinylphenylhydrazine. The protonated species undergoes a [3.3]-sigmatropic shift, as it would be called it today. The weak N–N bond is broken and a strong C–C bond established in a cyclic electron shift. The lost aromaticity is restored by prototropy in the next step. The addition of the amine function to the iminium ion gives rise to a dihydroindole, and elimination of ammonia affords the aromatic heterocycle.

Our cycloadduct with dimethyl fumarate harbors a fixed ene-phenylhydrazine system. On acid treatment, it started to move on the Fischer pathway. The thick bonds will help to recognize the [3.3]-sigmatropic rearrangement in this polycyclic system (Chart 17).33) After the intramolecular addition of the amino to the iminium function, the process got arrested. The aminal was isolated in 84% yield. Its structure was established by X-ray.34)

Why is the last step, the formation of the indole, blocked? On looking at the 8-membered ring of the tetracyclic indole, a derivative of the strained (E,Z)-1,3-cyclooctadiene is ident-
The inclusion of the planar nitrogen increases the strain further. The final gain in aromaticity cannot compensate the increase of strain energy.

Numerous cycloadducts of isoquinolinium N-phenylimide were subjected to acid treatment by Temme; high yields of the tetracyclic aminals were the products. The cycloaddition to dimethyl maleate afforded the two cis-diesters in a 10 : 90 ratio. The Fischer reaction of the minor cycloadduct did not even require acid catalysis (Chart 18).

To our amazement, the major isomer entered a completely different process with acid. When chemists study a reaction and vary the substrate, they expect generality. Then all on a sudden, like a thunderbolt, the generality fails.

In natural product synthesis, many chemists check new reactions by first using simple models. Woodward, the magician of organic synthesis, was a sworn enemy of model experiments. He commented once—half in joke:

“One finds that there are no general reactions. That’s the glory of chemistry—that it is an experimental science.”

A conversion which has been successful in simple molecules, might fail in the synthetically important case.

When the major cycloadduct of maleic ester was treated with HCl in methanol, bright yellow crystals of a compound C\textsubscript{24}H\textsubscript{22}N\textsubscript{2}O\textsubscript{6} were formed. Embarrassingly, it contained three carbon atoms more than the starting material; the NMR spectrum showed three different ester groups (Chart 18).

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Tony Durst, a postdoc from the University of Western Ontario, Canada, spent the year 1965 in Munich. He carried out the described experiment, and recognized the C\textsubscript{24} formula. The unexpected result of a sideline remained in the drawer for several decades, until a fascinating sequence of steps was brought to light.
compound is formed. What are the side products? What is the fate of the second molecule which has spent three C-atoms? The cracking of hard nuts is a favorite sport of many scientists.

When the dimethyl maleate adduct was treated with a low concentration of HCl, i.e., only a third equivalent of acid, an isomer was obtained, which turned out to be an isoquinoline substituted in position 1 by an α-anilinosuccinic ester group. Thus, the pyrazolidine ring was cleaved by β-elimination (Chart 20).

The key experiment, the eye-opener, was the treatment of that open-chain isomer with strong acid in the presence of 2,4-dinitrophenylhydrazine. The isoquinoline-1-acetic ester was isolated in 66% yield. The dinitrophenylhydrazone of glyoxylic acid methyl ester precipitated, and aniline was isolated from the mother liquor (Chart 20). Thus, the anil of methyl glyoxylate must be the original fragment.37)

This anil or—more correctly—its protonated form attacks the enamine group of a second molecule of the cycloadduct and converts it to the yellow C24 compound.

Indeed, a synthetic specimen of glyoxylic ester anil was capable of converting the cycloadduct into the yellow compound in acid medium. Since the anil is unstable, an experiment with methyl glyoxylate itself is recorded in Chart 21. The acid protonates the carbonyl oxygen, thus increasing its electrophilic character. The piperidino glyoxylic ester chloride38) produced 76% of the yellow compound; no acid is required here.37)

The second molecule of the dimethyl maleate adduct can be replaced by the cycloadducts of acrylonitrile or dimethyl fumarate; what matters now, is only the ene-hydrazine group as nucleophilic reagent. The reaction with the piperidino derivative of methyl glyoxylate provided the corresponding yellow products, as illustrated in Chart 21 by the nitrile.

A new problem is looming. The oxidation state of the aldehyde group in glyoxylic ester ends up with that of acetic ester in the C24 compound, and two hydrogen atoms of the pyrazolidine ring must be the reducing agent. How does this intramolecular redox reaction come about?

In a plausible scheme, the protonated glyoxylic ester anil binds to the β-position of the ene-hydrazine group. The iminium ion loses the β-proton; for simplicity, the proton is transferred to the anilino residue in Chart 22. The loss of aniline furnishes an α,β-unsaturated iminium ion. Removal of the 10β-proton establishes the aromatic isoquinolinium ion.

Finally, a formal proton migration from position 1 to the carbanionic side chain furnishes our yellow compound. The electron flow from the lower to the upper part of the molecule demonstrates the redox process.

Our cycloadducts are derivatives of 1,2-dihydroisoquinoline. The mechanistic postulate presented in Chart 22 is supported by the fine work of Brown, Dyke, and Sainsbury.39) A dimethoxy-1,2-dihydroisoquinoline reacted with benzaldehyde under acid catalysis (Chart 23). The not isolated intermediate eliminates water. Again, the upwards directed flow of electrons signals the intramolecular redox reaction; the side chain is formally reduced to benzyl by the hydrogen of the 1,2-dihydroisoquinoline ring.

The interaction of glyoxylic acid with N-methyl-1,2-dihydroisoquinoline constitutes a second example.

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Chart 24 summarizes the amazing story that is a drama in two parts. In the first, the stepwise cleavage furnished methyl isoquinoline-1-acetate and the anil of glyoxylic ester. The proton adduct of the latter converted a second molecule of dimethyl maleate into the yellow C24 compound was unique and did not find an analogue. Obviously, the success depends on a fine tuning of the rate constants of all reaction steps, especially between part 1 and part 2 of the reaction drama.

Scientists proudly present new synthetic methods of wide scope. The last chapter demonstrates just the opposite: the anatomy of a singular case. Still shadowy, the contours of new reactions are recognized.

Heterocyclic chemistry has many frontiers of active research. In the new millenium, heterocycles will be as important as ever.

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