'HRONICLES

EUROPEAN CONFERENCE ON THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

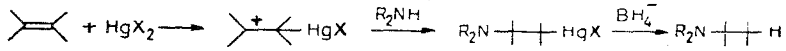
A. N. Kost

A conference on the chemistry of heterocyclic compounds, organized by the European Association of Chemists (EUCHEM), was held from April 24 to April 27, 1973, in the La Grande Motte health resort on the seacoast 9 km from Montpelier. This association holds annual or biennial conferences on the various fields of chemistry. Traditionally the conferences are functional in character, i.e., speakers from various countries are invited to speak on a selected problem in order to set forth the status of the problem and formulate the themes for discussion. Representatives of the scientific-research organizations, who pay for participation in the conference but do not present papers or reports, are invited to the conference. According to tradition, the co-workers of the organizer institution, who carry out the heavy organizational work, are present at the conference free of charge. Thus, the conferences assemble about 100-150 participants and, in addition, 15-20 speakers. No one presents any abstracts whatsoever, and the discussions are not printed. The papers take up (at the desire of the speaker) from 20 minutes to 1 hour. Each paper is followed by a discussion, which sometimes becomes quite prolonged. Thus these conferences recall our scientific schools with respect to the style of their operation.

The 1973 conference was organized by the University of Montpelier and consequently was headed by the dean of the chemistry faculty of this university, Professor R. Jacquier. There were 18 speakers, including six from France, three from Great Britain, one each from Denmark and Belgium, and two from the Federal Republic of Germany. In addition, the organizers invited speakers from the United States (three), the USSR (one), and the German Democratic Republic (one). There were about 60 participants with about another 30 co-workers of the University of Montpelier. Thus there were little more than 100 persons, and since not all of them were present for each paper (we note that the speakers were at all plenary sessions), about 50 persons were present at one time; this made it easy to carry out the discussions. Of the 60 participants mentioned above, there were representatives from Great Britain (four), the United States (three), Spain (two), Italy (two), Switzerland (three), Thailand (two), Burma (one), Holland (seven), and Belgium (one), while the rest were from France. Most of the participants were representatives of firms. For example, the leading chemists from the firms Ciba-Geigy, Sandoz, and Hoffman-LaRoche came from Switzerland.

The primary group of papers was concentrated around two problems: heterocyclization leading to nitrogen heterocycles, and the photochemistry of heteroaromatic compounds. The greater portion of the papers was linked with the interests of medicinal chemistry, although the biological action of the substances obtained was not directly discussed in any of them. The synthesis of interesting structures was of primary concern.

Professor A. Lattes (University of Toulouse) was the first speaker and reviewed his research on the use of aminomercuration and hydroxymercuration in the synthesis of heterocycles. It is known that mercury salts add to olefins to give an active carbonium ion that is capable of attacking the unshared pair of electrons of the oxygen or nitrogen atom to give, respectively, β-mercurated alcohols or amines. The mercuro group is then readily removed by the action of sodium borohydride; if the mercury atom is bonded to an asymmetrical carbon atom, it is removed with retention of the configuration.



Heterocyclization is possible when a double bond and an amino group are present in the same molecule. Thus, the corresponding pyrrolidine (II) is obtained from 5-aminopentenylbenzene (I), but up to 30% of

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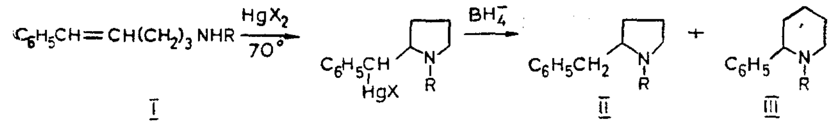
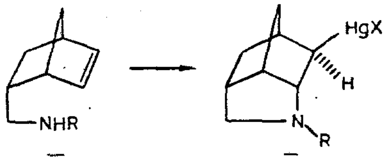
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 2, pp. 277-285, February, 1974.

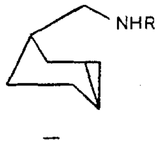


piperidine derivative III is formed simultaneously with ring expansion. The ring expansion proceeds during demercuration, since, judging from the PMR spectrum, the intermediate mercuro compound has a five-membered ring. The formation of five- and six-membered rings was also noted in the mercuration and subsequent reduction of 6-methyl-2-propylamino-5-heptene. However, if there are no substituents at the end of the double bond, the process takes place without isomerization of the radical. Thus 1-propylamino-3-butene and 1-propylamino-5-hexene are cyclized to 1-propylpyrrolidine and 2-methyl-1-propylpiperidine, respectively.

The reaction depends substantially on steric factors. Thus cyclization of amine IV gives only isomer V, while amine VI forms a mixture of five- and six-membered rings.

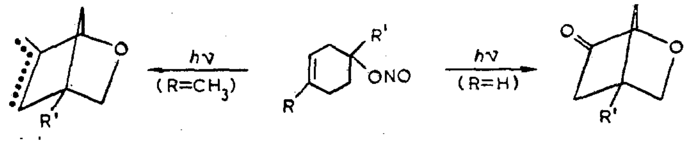


IV V

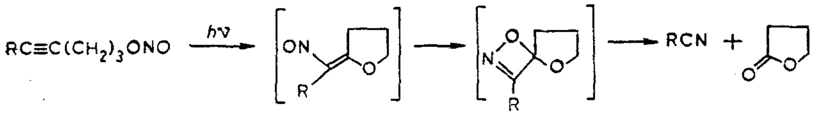


VI

The speaker also examined the photochemical cyclization of unsaturated nitrites.

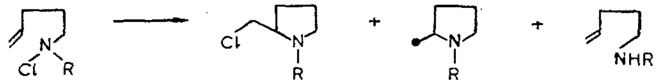


If a triple bond rather than a double bond undergoes attack, the intermediate is cleaved as in the Beckmann rearrangement.

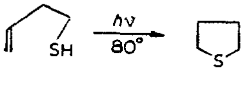


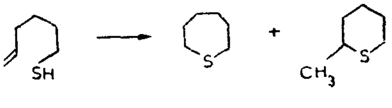
Similar heterocyclizations proceed during initiation with peroxides to give carbon–carbon or carbon–heteroatom bonds.

The Hofmann–Löffler reaction, which is based on the decomposition of N-chloroamines, is the most developed reaction in this direction. Here, the ratio of reaction products depends substantially on the solvent.



Heterocyclization of unsaturated mercaptans occurs similarly during photochemical initiation.

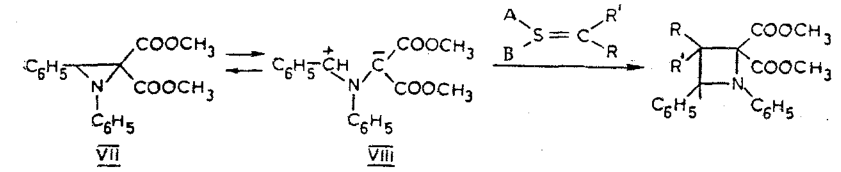




Primarily a seven-membered ring is formed from 5-hexenethiol at −65°C, while a six-membered ring is formed almost exclusively at +80°. The synthesis of bicyclic structures could be carried out similarly.

Professor R. Carrie (University of Rennes) reported that aziridine derivatives with strong electron-acceptor groups attached to the carbon atoms are capable of readily undergoing cleavage at the C–C bond rather than at the C–N bond. Actually, such structures react as ylides, interacting with both nucleophiles and electrophiles. For example, ester VII is stabilized as ylide VIII by the action of benzoic acid. Ylide

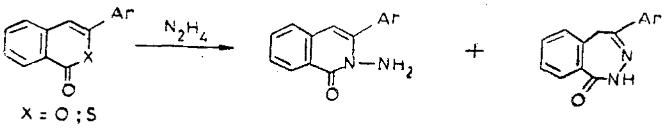
VIII readily reacts with Wittig reagents to give pyrrolines. Azetidines are obtained with ylides of tetravalent sulfur.



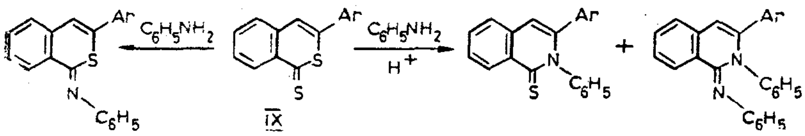
Professor C. W. Rees (University of Liverpool) discussed attempts to synthesize superaromatic structures of the benzoazetidine and cyclobutenopyridine type and the related chemistry of 1,2,3-triazanaphthalene. Attempts to obtain a four-membered ring in the benzene series by pyrolysis of o-azido ketones led to opening of the benzene ring, while oxidation of the corresponding hydrazones gave triazanaphthalene derivatives.

The paper presented by O. Buchardt (Copenhagen) was devoted to the photochemical transformations of N-oxides of the pyridine and benzopyridine series. He examined the mechanisms of reactions with ring contraction (formation of acylindoles from quinoline N-oxides) or ring expansion (formation of 1,3-oxazepines). In parallel fashion, he eastablished the formation of dimers, quinolone derivatives, etc., for benzopyridine derivatives. He also established that the oxazepine model is an intermediate in the photochemical formation of the pyrrole ring. Similar processes were followed in the pyridazine series.

In a comparatively brief paper, Professor N. Lozach (University of Caen) examined the instances of the ambiguous occurrence of reactions of sulfur analogs of isocoumarin. As in the case of the oxygen compounds, their hydrolysis proceeds with partial ring expansion.



The corresponding thione (IX) undergoes replacement of the thione group on reaction with aniline, but replacement of the ring sulfur atom occurs during proton catalysis.

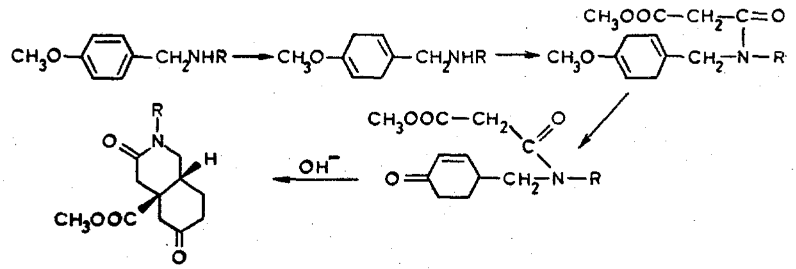


The reaction proceeds similarly but in a more complex manner if another heteroatom is introduced into the ring.

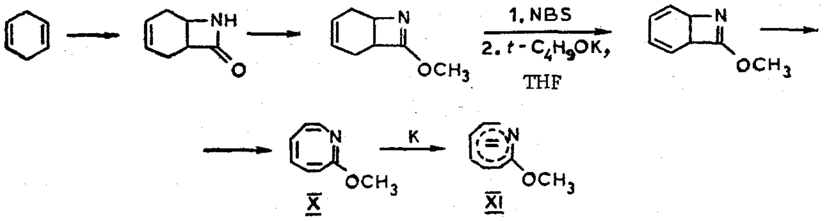
Surzur and Metzger from the University of Marseilles discussed the synthesis of five- and six-membered sulfur rings with two heteroatoms (one of them being a nitrogen atom) as a method for radical cycloaddition and as a method for chemical transformation of an already existing ring. In particular, Metzger focused attention on the steric requirements of substituents during the alkylation of thiazolidonethiones, evaluating the structures of the molecules both from the PMR spectra and by means of x-ray diffraction analysis; this made it possible to have independent information regarding the structures in the solid state and in solution.

H. Dorn from the Institute of Organic Chemistry of the Academy of Sciences of the German Democratic Republic presented a detailed paper that summarized his research on the synthesis of aminopyrazoles and their cyclization to pyrido- and pyrimidopyrazoles. He dealt separately with this method of aromatization of pyrazolines and pyrazolidones by cleavage of the corresponding tosyl derivatives.

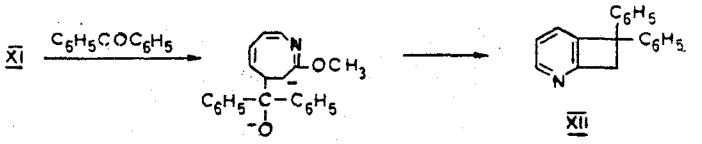
The American scientist G. Stork presented a short report on attempts to use the known method of alkylation of enamines (Stork alkylation) for the synthesis of yohimbine and its analogs. Stereospecific routes for the synthesis of two isomeric perhydroisoquinolines, one of which is based on the partial reduction of the benzene ring by the Birch method, were found:



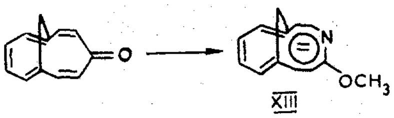
The American chemist L. A. Paquette found a quite general method for the synthesis of homoaromatic compounds in the heterocyclic series. The ability to undergo polarographic reduction was taken as the criterion of aromaticity. Dianion XI, which fulfills the requirements of aromaticity, was obtained by the action of potassium metal on azacyclooctatetraene (X). It displays a potential that corresponds to two-electron reduction and readily reacts with acids (to give 3,4- and, in part, 7,8-dihydro derivatives) and other electrophiles.



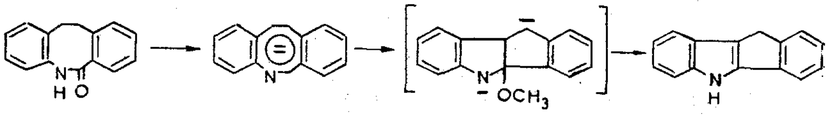
Ion XI readily adds benzophenone and then undergoes spontaneous conversion to cyclobutenopyridine (XII).



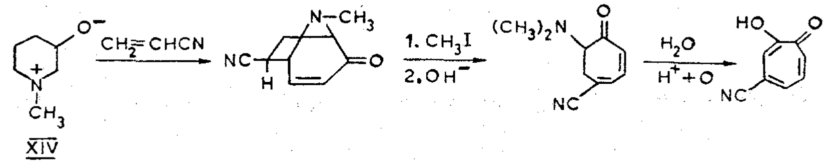
Homoaromatic structure XIII was similarly synthesized and characterized.



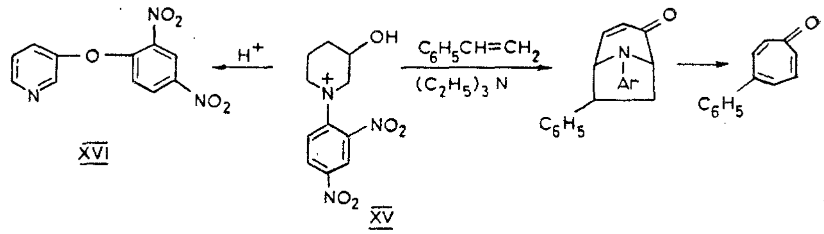
Doubly-charged ions condensed with the benzene ring can be stabilized with ring contraction.



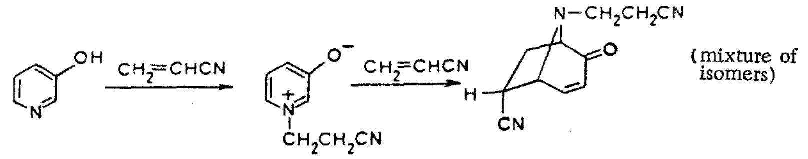
A. Katritzky (University of East Anglia), whose research on tautomerism is well known to us in the Soviet Union, at this time selected for his paper the ability of 3-hydroxypyridines and their benzo analogs to react in the dipolar ion form. He was able to show the 3-hydroxypyridine methiodide, after deprotonation, forms ylide XIV, which is capable of giving adducts with strong dienophiles (acrylic and maleic acid derivatives and dehydrobenzene). The subsequent transformations of the adducts proved to be a new method for the synthesis of tropolones. The reactions proceed similarly for 3-hydroxyisoquinolines, 1-phenyl-3-hydroxypyridinium ions, etc.



In passing, it was ascertained that the compound described in the literature as a 1-(dinitrophenyl)-3-hydroxypyridinium salt (XV) has ether structure XVI, into which this salt is very rapidly converted in the



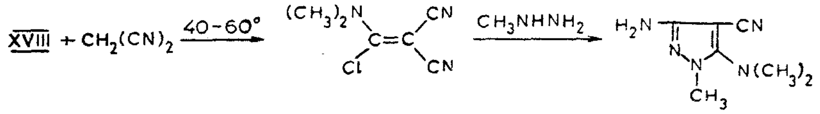
presence of protic solvents. Pure XV gives adducts with, for example, styrene. In a number of cases, quaternization of the pyridine ring is not necessary, for example:



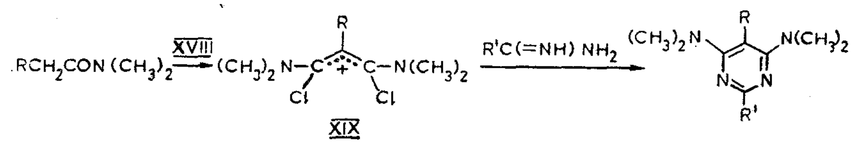
Similar reactions proceed for hydroxy compounds of the pyridazine, phthalazine, and cinnoline series.

$$(CH_3)_2NCSCl + Cl_2 \rightarrow \underset{XVII}{(CH_3)_2NCCl_3} \rightleftarrows \underset{XVIII}{(CH_3)_2\overset{+}{N}{=}CCl_2\;Cl^-}$$

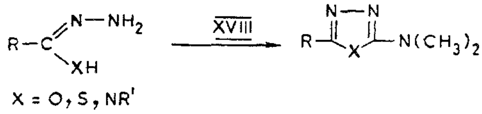
The Belgian scientist H. Viehe examined the synthetic possibilities that are offered by the use of the so-called "phosgenimmonium salts" as applied to heterocyclization. In 1957, N. N. Yarovenko reported that unstable substance XVII is formed by the action of chlorine on carbamoyl chloride. It was found that substances of the XVII type actually have salt structure XVIII. They spontaneously liberate CH_3Cl on storage, even at −180°, but one can work with them in situ just as easily as with ordinary reagents. Salt XVIII proved to be a more energetic reagent than the salt of Broderick and Vilsmeier. It reacts readily with various CH-acid compounds.



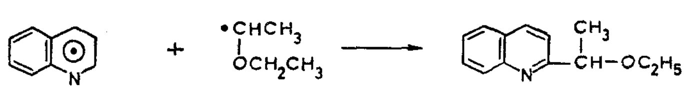
Under more severe conditions, even the α-methylene group of acid derivatives reacts to give an ion of the XIX type, from which diverse heterocycles can be synthesized:



Difunctional compounds form heterocycles with salt XVIII, for example:

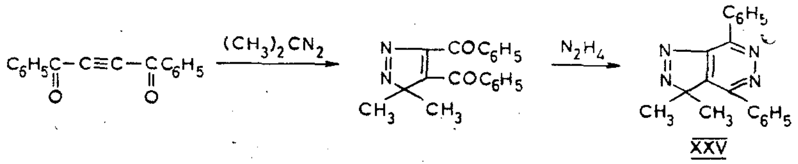


While Buchardt spoke on the photochemical transformations of N-oxides, A. Lablache-Combier (University of Lille) examined in detail the photochemical transformations of heterocycles of the pyridine, quinoline, and pyrazine type. It was found that irradiation of acridine brings about its reduction with partial alkylation by solvent molecules and dimerization. When the solvent was ether, he was able to fix the intermediate formation of free radicals. It is assumed that an n → π* transition in the pyridine molecule (or its analogs) is observed initially, and an ion radical is formed and is also attacked by a solvent radical. This is in agreement with the quantum-chemical calculations.

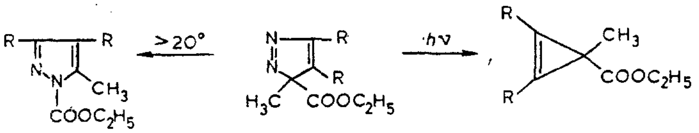


If the molecule is initially protonated, the process is facilitated, and alkylation proceeds even with methanol molecules.

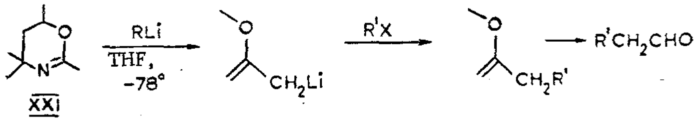
The reactions of isopyrazoles (i.e., pyrazolenines) were examined in a paper by M. Frank-Neumann (University of Strasbourg). During the synthesis of these compounds by the usual method – reaction of aliphatic diazo compounds with the corresponding olefins or acetylenes – he was able to find experimentally convenient methods for the preparation of structures with functional groups in the side chain. Special attention was directed to the synthesis of the corresponding compounds with a steroid grouping. He was able to synthesize 1H-pyrazolo[3,4-d]pyridazines (XXV) from diketones of the isopyrazole series.



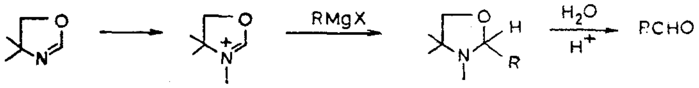
Migration of one of the geminal CH_3 groups to give pyrazoles usually occurs in the thermolysis of isopyrazoles (it is interesting that the $COOC_2H_5$ group migrated when there was competition between it and CH_3 groups). If this sort of structure is subjected to irradiation, nitrogen is preferably eliminated to give cyclopropene derivatives.



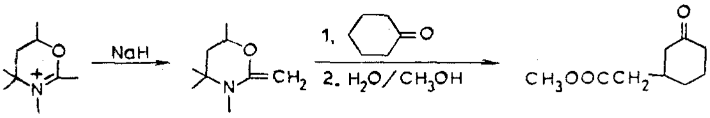
The American A. I. Meyers discussed a new method for the synthesis (including the stereospecific synthesis) of aliphatic aldehydes, ketones, and acids. Strictly speaking, this was not within the theme of the conference, but the research was of interest to synthetic chemists; formally, the method is based on the use of heterocycles, and it was therefore included in the program. 1,3-Oxazine derivatives of the XXI type are alkylated relatively readily through the lithium derivatives and form aldehydes after reduction and hydrolysis. The yields with organomagnesium compounds are somewhat lower. However, the yield can be raised substantially if the nitrogen atom is quaternized and the reaction is then carried out in hexametapol (hexamethylphosphoric triamide).



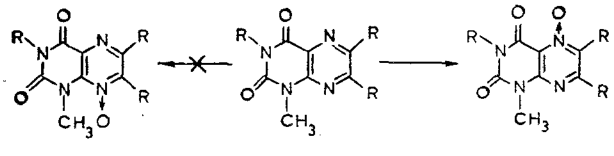
Good results were also obtained in the synthesis of branched structures; this made it possible to develop a new method for the preparation of branched ketones.



The method proved to be suitable in the terpenoid and steroid series.



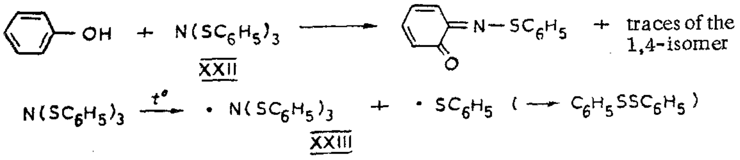
A search for methods for stereospecific synthesis was made on the basis of the same principle. Optically active norephedrine, from which an active oxazolidine was synthesized by reaction with propionic acid imino ester, was used initially. Subsequent alkylation and hydrolysis gave an optically active acid with an overall purity of only 29%. The use of optically active 2-amino-1-phenyl-1,3-propanediol, which is a by-product in the manufacture of synthomycin, was considerably more successful. This made it possible to obtain 2-methylhexanoic acid with a high degree of optical purity.



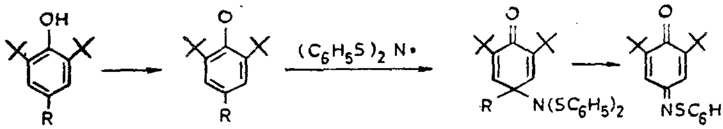
The establishment of the structures of various N-oxides that are formed in the direct oxidation of pteridines was the subject of the lecture by W. Pfleiderer (University of Konstanz). It was found that the nitrogen atom that is not shielded by a methyl group bonded to the nitrogen atom of the adjacent ring is oxidized preferably.

The joint application of the various spectra and alternative synthesis made it possible to also establish a number of principles of alkylation for both pteridines and simpler model structures of the pyrimidine and pyridazine type. A series of data on the direction of rearrangement of such N-oxides by the action of acetic anhydride was presented.

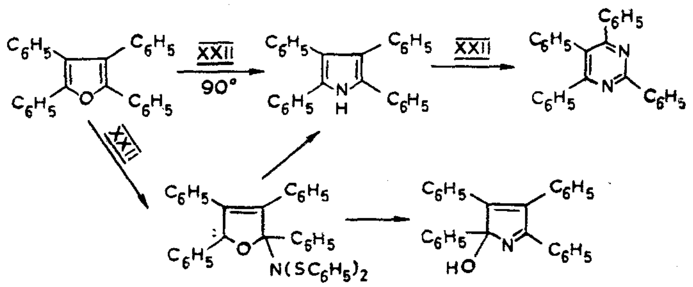
A long paper by the English Nobel Laureate D. Barton was devoted to syntheses by means of phenylsulfenamines. Tris(phenylsulfenyl)-amine (XXII), which is relatively readily obtained by the action of C_6H_5SCl on ammonia, readily thermally forms radical XXIII, which is capable of undergoing numerous reactions. Thus, it gives quinonimine derivatives on reaction with phenols or aromatic amines.



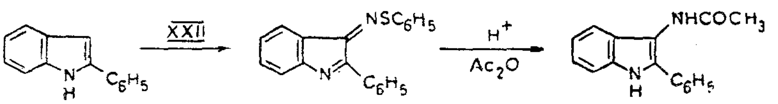
Sterically hindered phenols are attacked by this reagent with replacement of the group in the para position relative to the hydroxyl group. The reaction with 2,6-dialkylanilines proceeds similarly.



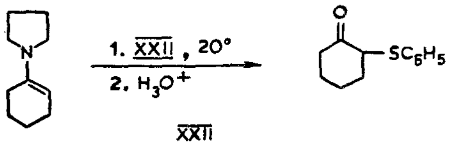
The reactions with five-membered heterocycles are interesting. Reagent XXII (or, more precisely, radical XXIII) is a quite strong electrophile and attacks the α-carbon atom of furan or pyrrole even if there is a substituent attached to it; replacement of the ring oxygen by nitrogen or ring expansion may occur.



Similarly, compounds of the indole series undergo oxidative amination with entry of the substituent into the 3 position.



In addition to radical processes, reagent XXII may react via the scheme of ionic reactions with structures in which there is a pair of π electrons, and a bond is formed with the sulfur atom (enamines, for example, react this way), or in which there is an unshared pair of p electrons, in which case a bond is formed with the nitrogen atom.



$$P(C_6H_5)_3 \xrightarrow[20^\circ]{\underline{\overline{XXII}}} (C_6H_5)_3P{=}NSC_6H_5$$

Thus the unusual oxidative amination reaction developed by Barton proceeds with a somewhat different orientation (for example, preferred entry of substituents into the ortho position even in the naphthol series) than other reagents give and is deserving of the serious attention of chemists doing research in the synthesis of heterocyclic structures.

A. N. Kost (Moscow University), on behalf of A. K. Sheinkman (Donetsk University) and himself, presented a review of hetarylation reactions, i.e., a review of methods for the direct introduction into an organic molecule of the residue of a heteroaromatic compound of the pyridine type and its benzo derivatives. The basic positions associated with the problem of hetarylation were touched upon in a paper by A. K. Sheinkman, which was published in Khimiya Geterotsiklicheskikh Soedinenii [Khim. Geterotsikl. Soedin., No. 1 (1974)]. It is also proposed that the texts of some other papers, which the authors have sent to the editorial staff of this journal, be published in more complete form.