



BRIEF REVIEW OF CONTRIBUTIONS TO EXPERIMENTAL ORGANIC CHEMISTRY

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1. INTRODUCTION AND BIOGRAPHICAL SKETCH

In previous years, I have published several accounts of my contributions to theoretical chemistry (mostly involving chemical applications of graph theory),¹⁻⁵ but none about experimental results, and therefore this article is intended to provide a brief review of my contributions to experimental organic chemistry. After having celebrated my 80th anniversary in 2011,⁴ I believe

that my experience may be a source of inspiration for young persons wishing to pursue a life dedicated to science and involving teaching and research. First, I have to provide in the following some autobiographical details.

It so happened that I had the chance of falling in love with chemistry and mathematics as a teenager. I was too young to become directly involved in the tragedies of the World War II, but my father (an electromechanical engineer) was mobilized in June 1942 and returned from the Russian front only late in 1943, so that my mother (an educator for

preschool children) had to face alone the evacuation from Bucharest after the first bombardments in April 1943. My parents encouraged me to learn foreign languages; French and German had been taught in high schools before 1945, and only Russian after that date. By reading books with a dictionary I learned French and German. After moving to Petroșani in 1945, I learned English by listening to BBC's English-by-Radio, which would have been politically dangerous in Bucharest. Having finished in Petroșani the last four years of high school, I registered in 1949 as a student at the Faculty of Industrial Chemistry in the Bucharest Polytechnic, attracted by the fame of Professor Costin D. Nenitzescu. His four-semester Organic Chemistry lectures were admirable and awesome, with his coworkers in white lab-coats sitting in the front row of the amphitheater, and with the carefully-planned experiments performed in front of the students to provide visual evidence about the reactions described by the formulas he was writing on the blackboard. He used to ask questions during his lectures, and therefore he knew which students were the most interested. Some of these students were asked by his coworkers (who were as dedicated to research as "the Magister") if they would like to join in research projects currently going on in the Laboratory of Organic Chemistry. I was one of these students. In 1953, for the first time since the war, graduate studies were resumed, following the USSR model with "aspirant" replacing the Ph. D. designation. Having succeeded in the competition for the aspirant-fellowship, I had the lowest salary among all my fellow schoolmates after they became chemical-engineers, but I was happy to do only research for three years. In 1955 I married one of these fellow schoolmates, Cornelia (Nelly), who, like me, had graduated as chemical engineer and would teach at the Bucharest Polytechnic till the mandatory retirement age.

Then several unexpected events followed: in 1956 together with about 200 young selected graduates in chemistry, physics and electronics who were offered the option of becoming future employees of the newly founded Institute of Atomic Physics (IFA) I attended one-year "qualification courses on atomic and nuclear physics", starting to work in IFA as a radiochemist in 1957 but continuing to be also an assistant-professor (later associate-professor) at the Organic Chemistry Department in the Bucharest

Polytechnic. Thanks to professor Horia Hulubei who was the Director of IFA and to professor Costin Nenitzescu, in 1963 I was elected as a corresponding member of the Roumanian Academy (only Nicolae Iorga had been elected at an earlier age, but then he soon was promoted to the status of titular member, whereas for me this happened only after the 1989 revolution). In 1967 I was appointed for three years as a Senior Research Officer at the International Atomic Energy Agency in Vienna, where I was in charge with editing monographs and organizing international conferences on radiopharmaceuticals and labeled compounds. I was also the liaison officer with the World Health Organization in Geneva for radiopharmaceuticals.

In 1970 Professor Nenitzescu passed away at the age of 69. Also in 1970, one of my wife's two brothers (the actor Septimiu Sever) and my only sister left Roumania illegally and independently of one another; as a consequence, invitations to travel abroad were seldom approved, and when occasionally this happened, my wife was never allowed to accompany me during the communist regime, which ended in December 1989.

Back in Bucharest after 1970, I grouped a small team of young coworkers in the Laboratory of Isotopically Labeled Organic Compounds in IFA, continuing also to teach at the Bucharest Polytechnic where I became a professor after 1970. With basic research possibilities becoming gradually more and more difficult, I gave up my position at IFA in 1974. Experimental conditions in the organic chemical laboratory also became more and more restricted, with hardships in acquiring documentation, chemicals, and instrumentation. It was thus easier to spend more time on theoretical research, based mainly on discrete mathematics. After 1990 when traveling abroad no longer had restrictions, I started to teach alternative semesters in Bucharest and at the Texas A&M University at Galveston, where I had been invited but was not allowed to visit earlier. For three years I served as Vice-president of the Roumanian Academy between 1995 and 1998. I retired from Bucharest and since 2000 I am a tenured professor of chemistry in USA, where there is no mandatory retirement age.

I had defended my Ph. D. thesis entitled "Reactions catalyzed by aluminum chloride" in 1959. Interestingly, Professor J. Andraos in Canada⁶ edited on the web tables of "Scientific genealogies of physical and mechanistic organic

chemists” based on the “Ph. D. instructor – student relationships” and in “Liebig’s scientific genealogy tree No. 4” one can see the sequence: J. Liebig–H. Will–A. Kekulé–T. Zincke–H. Fischer–C. D. Nenitzescu–A. T. Balaban. Another reference to the relationship C. D. Nenitzescu–A. T. Balaban may be seen on the web from www.ChemGeneration.com under ‘Chemistry Lessons’ followed by ‘Famous chemists in Central and Eastern Europe’.

As it may be seen when comparing the bibliographies of my theoretical (mathematical-chemical) and my experimental contributions, the former ones are often single-author papers, whereas this is seldom the case of the latter contributions. The explanation is simple: chemical-graph-theoretical papers are results of one’s own ideas, whereas papers presenting experimental data must perforce reflect team work: at the beginning of one’s career, papers are coauthored by the mentor and the persons responsible for analyses and spectral determinations; later when one has grouped a team of Ph. D. students, these coworkers become coauthors; and as one progresses enlarging the team, one’s experimental contribution decreases accordingly.

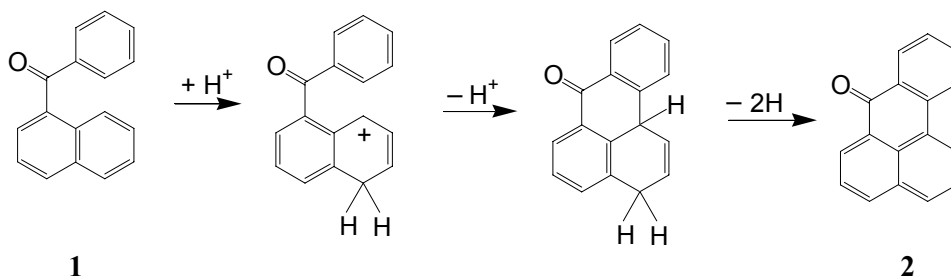
2. LEWIS-ACID CATALYZED: MECHANISM OF THE SCHOLL REACTION; 2,5-DIARYLOXAZOLE SYNTHESES

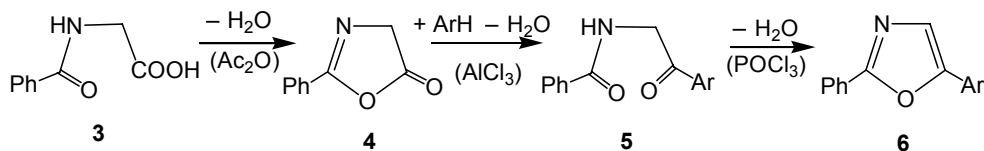
Unlike most of the pre-war scientists who had studied abroad (mostly in France or Germany) and had returned to Roumania as university professors, founding research schools with topics related to those they had during their studies, Nenitzescu invented new research fields such as the two “Nenitzescu indole syntheses”, explored the structure of acids from crude petroleum, and applied to aliphatic reactions the Friedel-Crafts catalyst (anhydrous AlCl_3) that had traditionally been used for aromatic substitutions.

The elucidation of the mechanism for the inter- or intramolecular dehydrogenative coupling of two aryl rings under the influence of aluminum chloride (the so-called Scholl reaction) was part of my Ph. D. Thesis. Under the influence of atmospheric water vapor, anhydrous AlCl_3 forms a small amount of the Brønsted superacid HAlCl_4 . With Nenitzescu, we showed that the reaction involves protonation of one aryl ring followed by an electrophilic substitution of another ring and by dehydrogenation of the dihydro-biaryl intermediate. We used another strong Brønsted acid, namely anhydrous crystalline benzenesulfonic acid, prepared by hydrolysis of benzenesulfonyl chloride followed by complete dehydration of the solution.⁷ The 23rd chapter in the Olah’s monograph on Friedel-Crafts and related reactions⁸ reviewed all dehydrogenating condensations of aromatics, in particular the Scholl reaction. For example, the formation of benzanthrene (**2**) from 1-benzoylnaphthalene (**1**) in the presence of AlCl_3 involves protonation, intramolecular electrophilic substitution and dehydrogenation as shown below.

This reaction and its variant using CuCl_2 as dehydrogenating agent⁹ were successfully used recently by Klaus Müllen for synthesizing many large polycyclic benzenoid hydrocarbons whose carbon skeleton is a fragment of graphene.¹⁰

We solved an intriguing contradictory report in the literature on the effect of AlCl_3 catalysts in a reaction between unsaturated azlactones and aromatic compounds which was shown to be due to the fact that American chemists had used perfectly anhydrous AlCl_3 ,¹¹ whereas chemists in Egypt¹² had allowed water vapor to convert it into the Brønsted superacid HAlCl_4 . Our paper on the influence of water in this reaction¹³ was published in 1962 together with Nenitzescu, his wife (Ecaterina Ciorănescu), and Dr. Ludmila Birladeanu (who later emigrated to USA during the 1970s and became a coworker of W. E. Doering at Harvard University).





Earlier, Drs. Ecaterina Ciorănescu and Ludmila Birladeanu¹⁴ had found that simple azlactones (4) could substitute electrophilically aromatics under the catalytic influence of AlCl₃ (acylaminoacylation of aromatics) affording acylaminoketones (5) which can be dehydrated to 2,5-diaryloxazoles (6). At that time, I had to prepare scintillators for detecting nuclear radiation in IFA, and I knew that 2,5-diaryloxazoles were among the best fluorescent solutes for liquid or plastic scintillators. It was not difficult to make the connection, and with Drs. Ciorănescu, Birladeanu and several coworkers from the IFA laboratory we explored the scope and limitations of this new oxazole synthesis.¹⁵ This area of research was continued till recently with Dr. Iosif Schiketanz at the Bucharest Polytechnic.¹⁶ The emission spectra of the strongly fluorescent 2,5-diaryloxazoles can be used for organic lasers.¹⁷

Bis-oxazoles can be synthesized from the corresponding bis-azlactones.¹⁸ An analogous synthesis of thiazoles was devised from thioazlactones.¹⁹ Cyclic isoimidium salts can function as reagents for a new electrophilic substitution of aromatics yielding β-aroilcarboxamides.²⁰

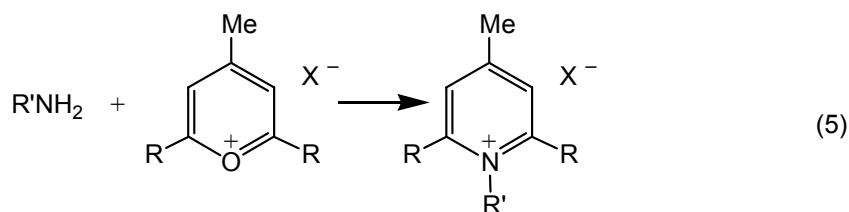
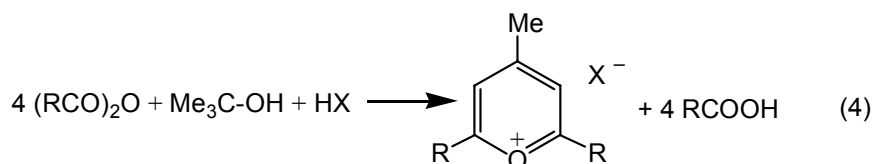
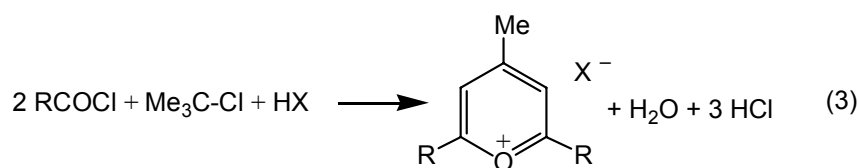
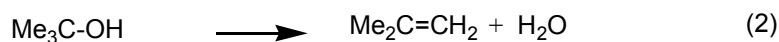
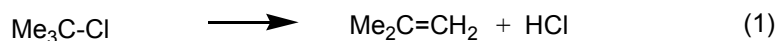
3. SYNTHESIS OF PERYLIUM SALTS, PYRIDINIUM SALTS AND PYRIDINES

At the same time when Koch and Haaf were finalizing their synthesis of carboxylic acids from alkenes, H₂SO₄, and CO,²¹ one of the topics of my Ph. D. thesis was the reinvestigation of the reaction between cycloalkanes and CO, for which a new mechanism was proposed.^{22,23} During the time of my work for the Ph. D. degree, I discovered serendipitously that alkenes with at least three carbon atoms such as propene, isobutene or α-methylstyrene can be diacylated affording perylium salts. Accidentally, when investigating the reaction between *tert*-butyl chloride, anhydrous aluminum chloride and carbon monoxide under pressure, a crystalline side-product was formed.²² At that time when physical methods were practically non-existent it took some time till the structure of that substance was established as 2,6-di-*tert*-butyl-4-methylperylium tetrachloroaluminate (with some chloroferrate from the impure catalyst).²⁴ In this remarkable reaction, five synthons are pieced together,²⁵ as I emphasized later in Hargittai's

journal *Chemical Intelligencer* (that regrettably no longer appears): the *tert*-butyl cation with carbon monoxide forms the pivaloyl cation, which diacylates isobutene that is in equilibrium with the *tert*-butyl cation. A gaseous alkene can be introduced into the reaction mixture as a halide with a Lewis acid (eq. 1 below) or an alcohol with a Brønsted acid (eq. 2), and the diacylation proceeds with acid chlorides and Lewis acids (eq. 3) or an anhydride and Brønsted acids (eq. 4). The perylium salt can then be converted by a primary amine into a pyridinium salt (eq. 5) or into a pyridine by ammonia, if R' = H. The only restriction for this reaction is that the 2- and 6-substituents must be identical; this reaction is the best one for obtaining alkyl-substituted perylium salts, and from them a large variety of other heterocycles or carbocycles.²⁶

It was shown that the reaction was general, and I published our results with Nenitzescu in 1959,²⁴ when simultaneously and independently Prail in England had also synthesized serendipitously perylium perchlorates. We exchanged correspondence, and decided to publish in 1961 side by side our more detailed results.²⁷ We became good friends with Percy Prail, and exchanged reciprocal visits. Percy has now one of the richest Romanian stamp collections in England. The formation of perylium salts by diacylation of alkenes was mentioned once as the 'Balaban reaction',²⁸ but is now known in the literature as the Balaban-Nenitzescu-Prail reaction,^{29,30} a name in agreement with the dual discovery in Bucharest and London.

With Nenitzescu at first, and then with my coworkers from IFA or from the Polytechnic (when I was not yet authorized to supervise Ph. D. students, professor Nenitzescu sent some of his students to me for joint work), we explored systematically the scope and limitations of the olefin diacylation.³¹⁻³³ The remarkable aspect of this reaction is that it had escaped observation for about 70 years, because earlier the numerous organic chemists who had acylated alkenes with Friedel-Crafts catalysts had looked only at the "organic layer" of the reaction mixture, discarding away the "aqueous layer" containing the perylium salts. A second chapter in Olah's monograph was published on "Aliphatic Acylation".³⁴



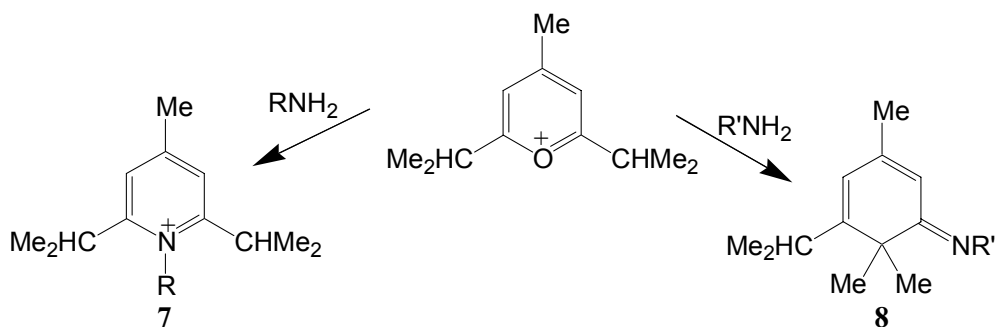
The regioselectivity of alkene diacylation is governed by kinetic and thermodynamic control, depending on the activity of the catalyst: with acid chlorides and tertiary pentyl chloride in the presence of the very active AlCl_3 or SbCl_5 Lewis acids, kinetic control predominates with the more reactive terminal alkene (2-methyl-1-butene) resulting in a trisubstituted pyrylium salt with a 4-ethyl substituent. By contrast, with catalysis by Brønsted or mild Lewis acids, thermodynamic control takes over and the diacylation product of the more stable 2-methyl-2-butene is an isomeric substituted pyrylium salt with 2,3-dimethyl substituents.³⁵ One should be aware that all these syntheses that were systematically investigated needed the tedious preparation of alkenes or tertiary alcohols by means of Grignard reactions; although most of these starting materials were commercially available, we could not afford to purchase them. Procedures for preparing 2,4,6-trimethylpyrylium salts were published in *Organic Syntheses* for the perchlorate,³⁶ triflate,³⁷ and tetrafluoroborate,³⁷ in *Organic Preparations and Procedures International* for 2,4,6-trimethylpyrylium sulfoacetate,³⁸ 2,4,6-triphenylpyrylium hydrogen sulfate,³⁹ and for 2,6-dimethyl-4-phenylpyrylium sulfoacetate.⁴⁰

Ammonia and primary amines convert very easily pyrylium salts into pyridines and pyridinium

salts, respectively. In 1969 with my coworker A. B. Susan we observed that N-alkyl-2,4,6-triphenylpyridinium halides with N-methyl groups are converted into methyl-halides on heating; with N-benzyl or substituted benzyl groups the analogous splitting of the alkyl group occurs even on recrystallization from ethanol affording benzyl ethyl ether.⁴¹ With Dr. Susan's emigration to USA, this line of research could not continue, but Professor Katritzky developed such reactions into an efficient method for converting primary amines into various other functional groups.⁴²

The pyrylium cation has the highest possible single-heteroatom perturbation due to the electronegativity of the oxygen heteroatom, second highest among all elements following fluorine; consequently pyrylium has a lower aromaticity than other 6-membered heterocycles and this explains why it is easily formed from acyclic precursors and also easily ring-opened by nucleophiles such as hydroxide (affording pseudobases), hydride⁴³ or cyanide (yielding 5-cyano-2,4-pentadien-1-ones).⁴⁴ Several recent reviews on aromatic heterocycles emphasize this special situation of pyrylium cations.⁴⁵

An observation about the fact that chalcones can function in acid medium as hydride acceptors led to improved yields in syntheses of pyrylium salts with aromatic substituents based on chalcones.⁴⁶

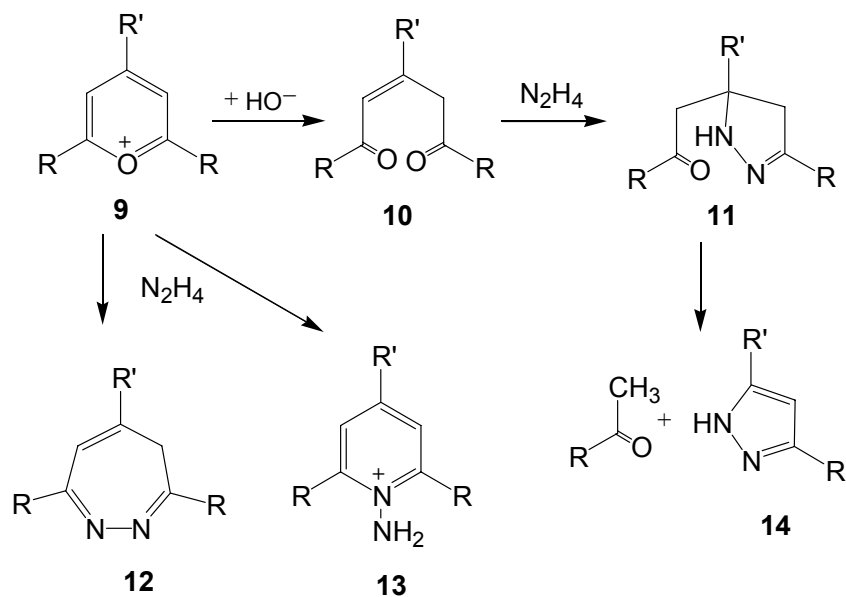


In a collaboration with Dr. Cornelia Uncuța from the ‘C. D. Nenitzescu’ Institute of Organic Chemistry of the Roumanian Academy, it was shown that even steric factors may cause deviations from the normal reaction course between pyrylium salts and primary amines: 2,6-diisopropyl-4-methylpyrylium reacts normally with most primary amines (RNH₂ with aromatic or small-alkyl groups R) yielding pyridinium salts (7), but a 6,6-dimethyl-1-cyclohexadiene-1-imine derivative (8) results from the reaction with isopropylamine which has a bulkier R' = *i*Pr group.⁴⁷ In both cases the pyrylium ring opens yielding a 5-alkylamino-2,4-pentadien-1-one derivative; in the former case the ring closure involves removal of a water molecule from the enolic OH group and the NH proton, but in latter case the isopropyl proton is involved (an analog reaction is the formation of phenols from 2,6-dimethyl(ene)-pyrylium salts with hot alkali hydroxides).⁴⁸

Pyrylium salts with aromatic or *tert*-butyl substituents in positions 2 and 6 (α -positions)

react with hydrazine forming 7-membered diazepine rings (12),⁴⁹ but 1,5-enediones (pseudobases of 2,4,6-triarylpyrylium salts, 10) afford 2-phenacylpyrazolines (11).⁵⁰ In a C–C bond splitting reaction driven by aromatization, these compounds separate into an acetophenone derivative and a pyrazole (14). An analogous reaction takes place on treating pyrylium salts with arylhydrazines, and our publication⁵¹ settled a long controversy about the structure of ‘pyranolhydrazides’. Proton NMR spectra were obtained when I was in Vienna, and they were very helpful for structural assignments.⁵²

The reaction of pyrylium salts with hydroxylamine affords pyridine-N-oxides as shown in two almost simultaneous publications from us²⁴ and from Professor Ernst Schmitz’s laboratory.⁵³ Stable 2,4,6-triaryl-pseudobases react similarly with hydroxylamine yielding isoxazoline derivatives, and an analogous C–C bond fission affords isoxazole and acetophenone derivatives.⁴⁹



At slightly basic pH values aqueous solutions of pyrylium salts add hydroxide anions yielding 1,5-enediones (pseudobases) which are stable when prepared from 2,4,6-triarylpyrylium, but when derived from alkyl-substituted pyrylium cations, they undergo rapid intermolecular condensations or polymerizations; 2,6-dialkyl(ene) pyrylium salts afford phenols with boiling sodium hydroxide by intramolecular condensation.⁴⁸ By contrast, pyridinium salts are stable in basic media, and they may have biological activities as will be shown in following sections. In neutral or even weakly acidic media, pyrylium anhydrobases (methylenepyryrans) exist in equilibrium with pyrylium salts.

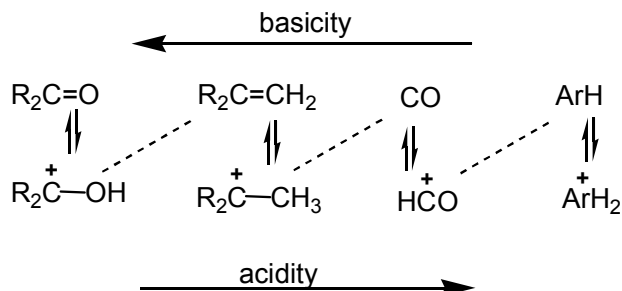
An extensive investigation of various physical properties of pyrylium salts could be made once we had prepared a large variety of such salts: electronic absorption spectra (UV-Vis);⁵⁴ infrared spectra;⁵⁵ ¹H-NMR spectra;⁵⁶ ¹³C-NMR spectra;⁵⁷ mass spectra;⁵⁸ electrochemical reduction potentials;⁵⁹ laser solute activity;⁶⁰ and charge-transfer spectra of salts with polarizable anions such as iodide, thiocyanate or selenocyanate.⁶¹ When we lacked the necessary instrumentation, we sent our samples to colleagues in other laboratories in Roumania (V. E. Sahini for electronic absorption spectra) or abroad and thus we published the results with chemists in Britain (A. R. Katritzky, L.E. Sutton), Germany (V. Wray), France (C. Rullière), USSR (V.I. Minkin), and USA (C. Djerassi).

Our observation about the fact that the bands in UV-Vis spectra were influenced differently by substituents in positions 4 from the effects of α -substituents were later confirmed by other research groups,⁶² which adopted our notation (x -band, y -band) for electronic transitions. A brief remark on NMR spectra is needed here: since NMR instruments were then the most expensive pieces of equipment, they were under supervision of qualified scientists, who interpreted the spectra and co-authored the articles; I have therefore to acknowledge the valuable contributions of Drs.

Mircea D. Gheorghiu, Miron T. Căproiu, Constantin Drăghici and Filip Chiraleu.

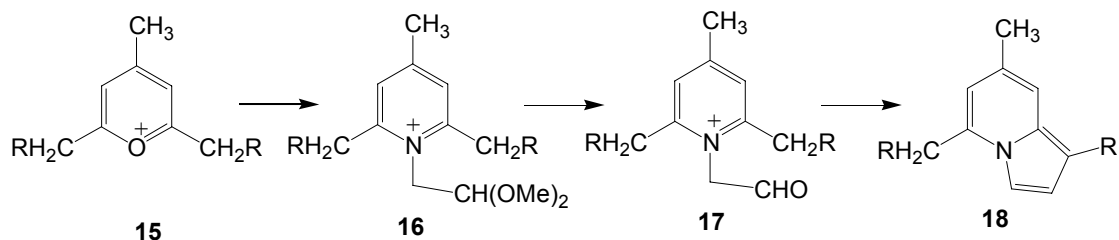
The fact that the chemical shifts in ¹H-NMR spectra differ markedly in 2,4,6-trimethylpyridinium salts having N-aryl groups depending on the type and size of the aryl substituent enabled me with my Ph. D. student Antonie Dinculescu to propose a simple method for evaluating the ring current in the aryl group by means of the difference between chemical shifts of α - and γ -methyl protons.⁶³ With him we prepared and patented in Roumania many pyridinium salts with potential biological activities. With him and coauthors from Halle (Germany) and Rostov-on-Don (Russia) we published the only existing book on pyrylium salts.⁶⁴ With Werner Schroth (Halle) I co-authored the chapter on pyrylium salts in the Houben-Weyl monograph in German; for the English updated versions, I collaborated with my son (Teodor-Silviu Balaban).⁶⁵ I was invited on several occasions to present lectures or to write chapters in edited books on pyrylium salts as conjugated five-carbon synthons,⁶⁶ and to contribute with monographs in Paquette's *Encyclopedia of Reagents for Organic Synthesis*.⁶⁷

In 1962 I published a theoretical generalization of heterolytic reactions⁶⁸ explaining the fact that the Gattermann-Koch reaction of carbon monoxide and aromatics is an electrophilic substitution involving the formyl cation (protonated CO), whereas the Koch-Haaf reaction between CO and alkenes involves the protonated alkene: the *weaker acid-base pair* (specified by the dashed line) reacts in both cases. In the formulas indicated below, the lower row contains conjugated acids of the upper row; reactions proceed between partners according to the dashed lines. The scheme below includes also the formation of 4,4-dimethyl-1,3-dioxane from isobutene and two moles of formaldehyde (Prins reaction). Aromatic alkylation and hydroxymethylation (or the analogous chloromethylation) are also electrophilic substitutions of ArH, involving as in the preceding cases the *weaker acid-base pairs*.



4. SYNTHESIS OF INDOLIZINES

Among the various intramolecular reactions of pyridinium salts that can be exploited to yield other heterocycles, we used the pyridinium salt (**16**) formed from pyrylium salts and aminoacetaldehyde dimethyl acetal, which is



hydrolyzed by aqueous NaHCO_3 to the aldehyde (**17**). Intramolecular dehydrating condensation with a 2-methyl(ene) group affords the substituted indolizine (**18**), again in collaboration with Dr. A. Dinculescu and my son.⁶⁹

5. ISOTOPICALLY LABELED COMPOUNDS

In IFA, the Laboratory of Isotopically Labeled Organic Compounds was in charge of handling stable and radioactive isotopes for use in research and as radiopharmaceuticals. By using ^{14}C -carboxyl-labeled acetyl chloride, we prepared by alkene diacylation ring-labeled pyrylium salts and then pyridines or pyridinium salts.⁷⁰

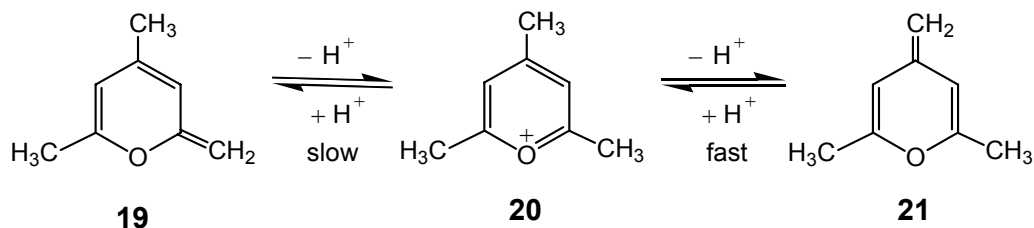
As mentioned earlier, anhydrous aluminum chloride forms a superacid with an equimolar amount of water. It was shown in collaboration with Dr. Constanța Mantescu that tritiated water in the presence of anhydrous aluminum chloride can be used for tritiating arenes, alkanes, RNA bases, amino acids and peptides.⁷¹

6. ISOTOPE EFFECTS USING PYRYLIUM SALTS AND PYRIDINES

We prepared with Dr. Cornelia Uncuța ^{13}C -labeled pyrylium salts that were used in collaboration with Professor R. I. Van Etten and Dr. J. M. Risley (USA) for following via ^{13}C -NMR spectra the kinetics of the isotopic exchange between pyrylium salts and ^{18}O -labeled water at a buffered pH. This exchange proceeds via reversible addition of hydroxide anions and

formation of a pseudobase. The NMR chemical shifts of a ^{13}C -carbon atom next to an ^{18}O atom and ^{16}O atom are different, so that by starting with $\text{CH}_3\text{-}^{13}\text{COCl}$ and monoacylating mesityl oxide or diacylating isobutene it was possible to obtain the targeted singly or doubly ^{13}C -labeled 2,4,6-trimethylpyrylium salts, respectively.⁷²

By means of IR absorption spectra, I had observed in 1962⁵⁵ the reversible hydrogen isotopic exchange between deuterium oxide and α (2,6-positions) or γ (4-position) side-chains of pyrylium salts (methyl, methylene, or methine),⁷³ and this fact had helped later in the investigation of some physical properties of these salts. The mechanism involves deprotonation to methylenepyrans (anhydrobases). The observation that the exchange rate is about ten times higher for the γ -methyl than for the α -methyl groups in 2,4,6-trimethylpyrylium (**20**) could be rationalized on the basis of quantum-chemical calculations published in collaboration with Paul Schleyer,⁷⁴ which showed that the symmetrical 2,6-dimethyl-4-methylenepyran (**21**) is more stable than the isomeric 4,6-dimethyl-2-methylenepyran (**19**). This kinetic trend could be reversed by stabilizing the α -methylene pyran intermediate via extended conjugation in α -benzylpyrylium salts.⁷⁵



With extra substituents in 3- or in 3- and 5-positions, the kinetics of deuteration can differentiate between 2, 4, and 6-trialkyl groups. Interestingly, the above-mentioned calculations⁷⁴ also provide an explanation why the α,γ -regioselectivity for the deuteration of 1,2,4,6-tetramethylpyridinium salts is opposite to that observed for pyrylium salts. The kinetics of deuteration for isopropyl side-chains ($\text{CHMe}_2 \rightarrow \text{CDMe}_2$) is easy to follow by measuring the time-varying $^1\text{H-NMR}$ intensity of the Me_2 signal (a larger doublet caused by the proton, and at its center a narrow triplet caused by the deuterium atom). We prepared also isotopomers of the unsubstituted pyrylium cation and published a detailed assignment of the vibration modes.⁷⁶

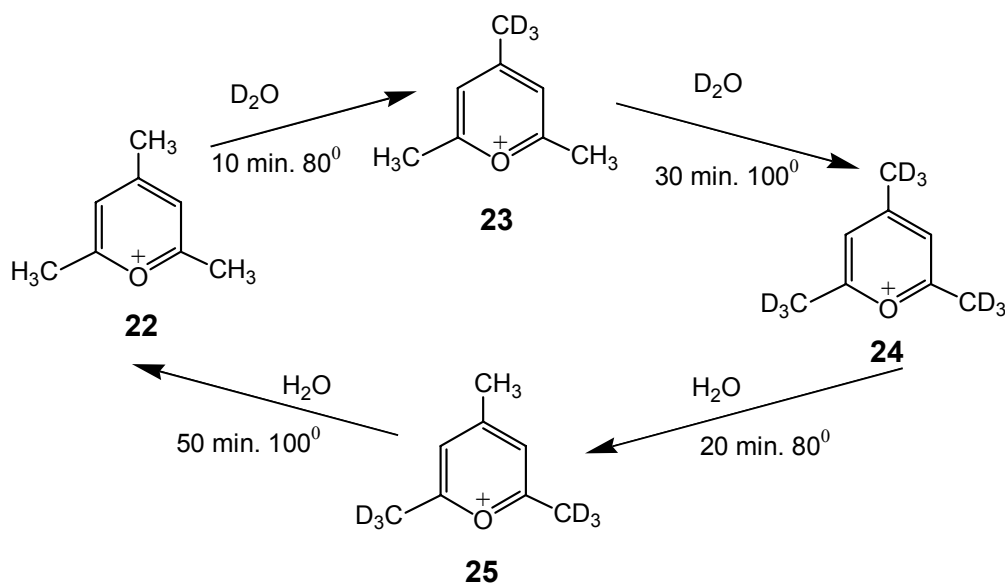
By reaction with cold ammonia, the 2,4,6-trimethylpyrylium cation (**22**) is converted quantitatively into sym-collidine conserving any deuteration of alkyl side-chains. On using regioselectively deuterated 2,4,6-trimethylpyrylium salts (either in α , **25**, or in γ , **23**, or for all methyl hydrogens as in **24**) one can obtain the corresponding pyridine derivatives. It was exciting to observe that these pyridinic isotopomers evidenced different secondary isotope effects on interacting with electrophilic probes that differentiated between electronic and steric effects.⁷⁷ In methyl-deuterated isotopomers, both the increase of basicity (due to the slightly higher electron-donating effect) and the reduction of steric shielding (due to the slightly reduced size) of CD_3 groups relative to CH_3 groups contribute to increasing the interaction with electrophiles.

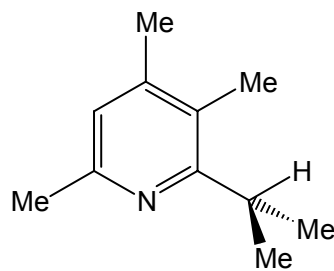
However, protonation evidences no sensitivity to steric factors, whereas coordination of lanthanide shift reagents (LSRs) reveals no sensitivity to increased basicity. In collaboration with Dr. Christian Roussel from the University of Marseille (France), we showed that the rate of quaternization with methyl iodide has almost equal contributions for the electronic and steric effects.⁷⁸

I reviewed these aspects in two book chapters, remarking that whereas the protonation and coordination with LSRs were chemical equilibria, the quaternization was a kinetically-controlled process.⁷⁹ Remarkably, our simple organic synthetic approaches were able to discriminate among steric and electronic components of secondary isotope effects.

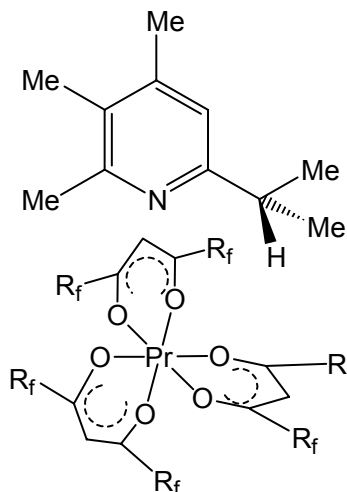
7. A NON-NUCLEOPHILIC PYRIDINE DUE TO A DOUBLE JANUS EFFECT

Freely rotating isopropyl groups offer two kinds of faces, like the mythological god Janus who looked both towards the past and the future, hence the name Janus group effect. A face of isopropyl groups is *tert*-butyl-like, associated with a considerable steric effect, and another one is ethyl-like. We had tested this effect in two isomeric substituted pyridines, 2-isopropyl-3,4,6-trimethylpyridine (**26**) and 6-isopropyl-2,3,4-trimethylpyridine (**27**).





26



27

It had been shown earlier that lanthanide shift reagents, LSRs, such as $\text{Eu}(\text{dpm})_3$, $\text{Eu}(\text{fod})_3$, $\text{Pr}(\text{dpm})_3$ or $\text{Pr}(\text{fod})_3$, complexed normally with pyridines substituted in α -positions (2 and 6) with one methyl and one isopropyl group, but not with those having one methyl and one *tert*-butyl group.⁸⁰ In other words, it was found that there was normal complexation of such LRSs with the pyridine (**27**) where the isopropyl group could rotate freely, but there was practically little complexation of any LSR with the isomeric pyridine (**26**) where the isopropyl was constrained (by buttressing due to the neighboring methyl group) to turn its *tert*-butyl-like face towards the site of complexation with the LSR. Starting from this observation, a simple synthesis was devised for a new non-nucleophilic base, using inexpensive reagents (triethylcarbinol, isobutyric anhydride, and 60% hexafluorophosphoric acid): we obtained in good yield a pyrylium salt which with ammonia yields the target 4-ethyl-2,6-diisopropyl-3,5-dimethylpyridine. In this reaction, a sufficient amount of isobutyric anhydride needs to be present both for the diacylation, and for binding the water that comes with the 60% hexafluorophosphoric acid (5.4 moles of water for each mole of HPF_6). Triethylcarbinol (3-ethyl-3-pentanol) was selected in this synthesis because its dehydration affords a single alkene, namely 3-ethyl-2-pentene, and therefore a single pyrylium salt is obtained. Neither $\text{Eu}(\text{fod})_3$ nor $\text{Pr}(\text{fod})_3$ show any complexation with 4-ethyl-2,6-diisopropyl-3,5-dimethylpyridine, which behaves with LSR just as 2,6-di-*tert*-butylpyridine and its 4-methyl derivative. In this case, both isopropyl groups are *tert*-butyl-like due to a double Janus effect.⁸¹

Earlier we had reported a synthesis of the non-nucleophilic base 2,6-di-*tert*-butyl-4-methylpyridine from its pyrylium analog obtained by diacylation of isobutene (actually, *tert*-butyl chloride that is easier to handle) with pivaloyl chloride in the presence of tin tetrachloride.⁸² Other Lewis acids cause decarbonylation of pivaloyl chloride, but an expensive Brønsted acid (triflic acid) can also be employed. The work-up is tedious, and the yields are not high. It has long been known that 2,6-di-*tert*-butylpyridine or 2,6-di-*tert*-butyl-4-methylpyridine, which are available commercially at present at a fairly high cost, are non-nucleophilic bases. This fact makes them useful for many applications, e.g. as proton traps for living cationic polymerizations, inhibiting chain branching and lowering the polydispersity. Benzylic triflates can be prepared with triflic anhydride in the presence of 2,6-di-*tert*-butylpyridine and are used in-situ for the living polymerization of tetrahydrofuran. Highly isotactic poly(isobutyl vinyl ether) was obtained with titanium-based Lewis acids and 2,6-di-*tert*-butyl-4-methylpyridine. Such pyridines distinguish between Brønsted acids, which are able to protonate them, and Lewis acids such as BF_3 or SO_3 , which do not interact with them. Rate constants between vinylic cations and 2,6-di-*tert*-butylpyridine are the lowest among all pyridines. Enolizable aldehydes and ketones afford enolic triflates with triflic anhydride and these non-nucleophilic bases; such enolic esters are important in carbohydrate research; other such esters can be used for palladium-catalyzed couplings.

8. USES OF NEW PYRIDINIUM SALTS: IONIC LIQUIDS AS NON-VOLATILE SOLVENTS AND CATIONIC LIPIDS AS GENE TRANSFER AGENTS

Pyrylium salts with two α -substituents with linear chains of 3 to 5 carbon atoms have low melting points. I had observed that 2,6-di-*n*-propylpyrylium perchlorate gave a liquid hydrate at room temperature, which became crystalline when anhydrous.⁸³ The crystalline 2,4,6-trimethylpyrylium tetrachloroferrate becomes a liquid on adding aromatic hydrocarbons or chloroform. At present, N,N'-dialkylimidazolium salts and 1-alkylpyridinium salts obtained by quaternization are the most used ionic liquids.⁸⁴ Another class of promising ionic liquids includes pyridinium salts with low melting points obtained from pyrylium salts and primary amines. We can have 1, 2, or 3 medium-sized linear alkyl groups that can be varied, in addition to the anion. When a 2-alkyl-4,6-dimethylpyrylium salt is obtained by acylating mesityl oxide, one can react it with a short- or medium-sized alkylamine. Alternatively, one can obtain by diacylation of isobutene pyrylium salts with two identical long-chain α -alkyl groups to which one can add a third alkyl from the alkylamine when converting this salt into a pyridinium salt.⁸⁵ Another possibility is to replace the alkylamine by a *para*-alkylaniline with a linear alkyl group.⁸⁶ Theoretical aspects of ionic liquids in terms of the N-alkyl-chain length were examined in a collaboration with professors Douglas J. Klein and Norman H. March.⁸⁷

A USA patent was obtained for cationic lipids as transfection (gene transfer) agents prepared from 2,4,6-trimethylpyrylium salts by reacting them with aminopropanediol, followed by esterifying or etherifying the two diol groups so that they bear long linear alkyl groups.⁸⁸ These cationic lipids are known to become intercalated into membrane bilayers, and are able to compact the DNA polyanion so that it can be carried into cell nuclei. With William A. Seitz and Marc Antoniu Ilieș, my ex-Ph. D. student who is now an assistant professor at Temple University, Philadelphia, we reviewed the known cationic lipids, pointing out that unlike viral vectors that are the most employed at present because they have a high efficiency, cationic lipids do not cause immune reactions, and can carry much larger amounts of genetic material.⁸⁹ A different approach was based on preparing pyrylium salts with one long-chain α -alkyl substituent which was then

converted by reaction with a long-chain alkylamine into a pyridinium salt. Our pyridinium-based cationic lipids were tested on various cell lines and live animals, and were found to have promising activities against several types of human cancer cells.⁹⁰ A recently published single crystal X-ray diffraction study of a cationic lipid with hexafluorophosphate anions revealed the interesting crystal packing of such ionic molecules.⁹¹

9. FURTHER USES OF PYRIDINIUM SALTS: TRIARYL-ETHYLENIC ANTI-TUMOR AGENTS AND CARBONIC ANHYDRASE INHIBITORS

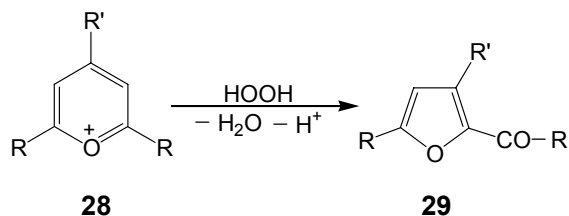
A co-authored book on cancer genesis and prevention⁹² and a book chapter on alkylating agents as chemotherapeutic compounds (written in collaboration with Drs. Nicolae Voiculeț and Ion Niculescu-Duvăz)⁹³ served as preambles for synthesizing with Dr. Octavian Stănciuc new pyridinium cations attached to tamoxiphene or clomifen moieties, yielding compounds which were designed to be potential non-steroidal antiestrogens, active against hormone-dependent tumors in breast cancers.⁹⁴

At present the "highest scientific authority" on carbonic anhydrase (CA) isoforms is Claudiu T. Supuran, who is now a professor at the University of Florence in Italy. Our collaboration began in Bucharest by exploring new pyrylium salts⁹⁵ and the biological activity of pyridinium salts formed from them and various primary amines.⁹⁶ Although some of these pyridinium salts were found to activate certain CA isoforms,⁹⁷ specially designed pyridinium salts proved to be specific inhibitors of the human carbonic anhydrases (hCAs) that distinguish cancer cells from ubiquitous hCAs offering promise for the fight against cancer.⁹⁸ Attempted quantitative structure-activity relationships (QSARs) for the bioactivity of hCA inhibitors using topological indices had so far limited success.⁹⁹

10. 2-ACYLFURAN AND 2-OXAZOLIN-4-ONE DERIVATIVES

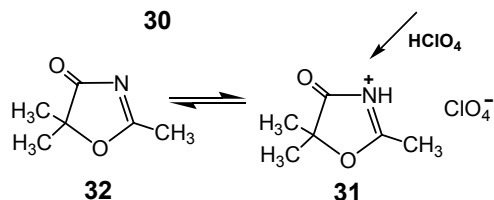
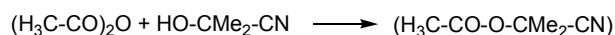
Although Dilthey had described the ring-contraction of 2,4,6-triphenylpyrylium cations (**28**, R = R' = Ph) affording 2-benzoyl-3,5-diphenylfuran, he did not recognize the generality of this reaction. On treating 2,4,6-trimethylpyrylium

salts (**28**, R = R' = Me) with hot hydrogen peroxide, 2-acetyl-3,5-dimethylfuran (**29**, R = R' = Me) results in good yield, and various other pyrylium salts behave similarly.¹⁰⁰



An interesting observation came from the colors of hydrazones which at that time were the usual means for identifying new compounds, when IR and NMR spectra were not available. Distinctly different shades of orange or red differentiated 2,4-di-, 2,6-di- or 2,4,6-tri-nitrophenylhydrazones in the presence or absence of steric hindrance, which affected the planarity (and consequently the conjugation) of these molecules.¹⁰¹ In a collaboration with Professor Shuikin (Moscow) it was found that our 2-acylfurans on catalytic hydrogenation underwent ring expansion reforming the pyran ring.¹⁰² The conformation of the planar 2-furyl ketones was first analyzed by means of ¹H-NMR spectroscopy in the presence of lanthanide shift reagents,¹⁰³ and the results were then checked by X-ray diffraction.¹⁰⁴

In an attempt to prepare 4-cyano-2,6-dimethylpyrylium perchlorate by diacetylating methacrylonitrile with acetic anhydride, only polymers were obtained. However, from acetone cyanohydrin (**30**), acetic anhydride and perchloric acid, a crystalline perchlorate was obtained in high yield, but it proved to be an unexpected perchlorate of 2,5,5-trimethyl-2-oxazolin-4-one (**31**) which with pyridine afforded 2,5,5-trimethyl-2-oxazolin-4-one (**32**).¹⁰⁵



Whereas all experimental results described so far can be traced back to my Ph. D. work plus my interest in isotope chemistry, I also opened up new avenues in experimental chemistry, to be described below, in addition to graph-theoretical work which

became progressively dominant as conditions for performing experimental work in Roumania deteriorated progressively during the 1970s and 1980s owing to lack of chemicals, spectroscopic instrumentation, and scientific documentation.

11. OLEFIN METATHESIS AND RING-OPENING POLYMERIZATION OF CYCLO-OLEFINS

My interest in homogeneous catalysis prompted me to propose the recently discovered olefin metathesis and ring-opening polymerization of cyclo-olefins as research area to Dr. Valeriu Drăguțan from the Institute of Organic Chemistry of the Roumanian Academy. Conditions for carrying out extensive experimental work were, however, unfavorable except for some contributions by Professor Mihai Dimonie from the Bucharest Polytechnic. We reviewed, however, the literature in the first book that was published in 1981 on this topic in Roumanian; our efforts for an English translation took a long time, and the corresponding expanded and updated English version was published by Wiley in 1985,¹⁰⁶ a short time after another book by K. J. Ivin had appeared in English (Academic Press).¹⁰⁷ Lately, with Valeriu and his wife, Ileana Drăguțan, we continued to update in *Platinum Metals Review* the progress in this area.¹⁰⁸ At present, due to newer experimental findings of R. R. Schrock and R. Grubbs (Nobel Prize for Chemistry 2005) metathetic ring-closing reactions of 1,ω-diolefins have become a precious synthetic method in organic chemistry.¹⁰⁹

12. STABLE NITROGEN-CENTERED PUSH-PULL FREE RADICALS

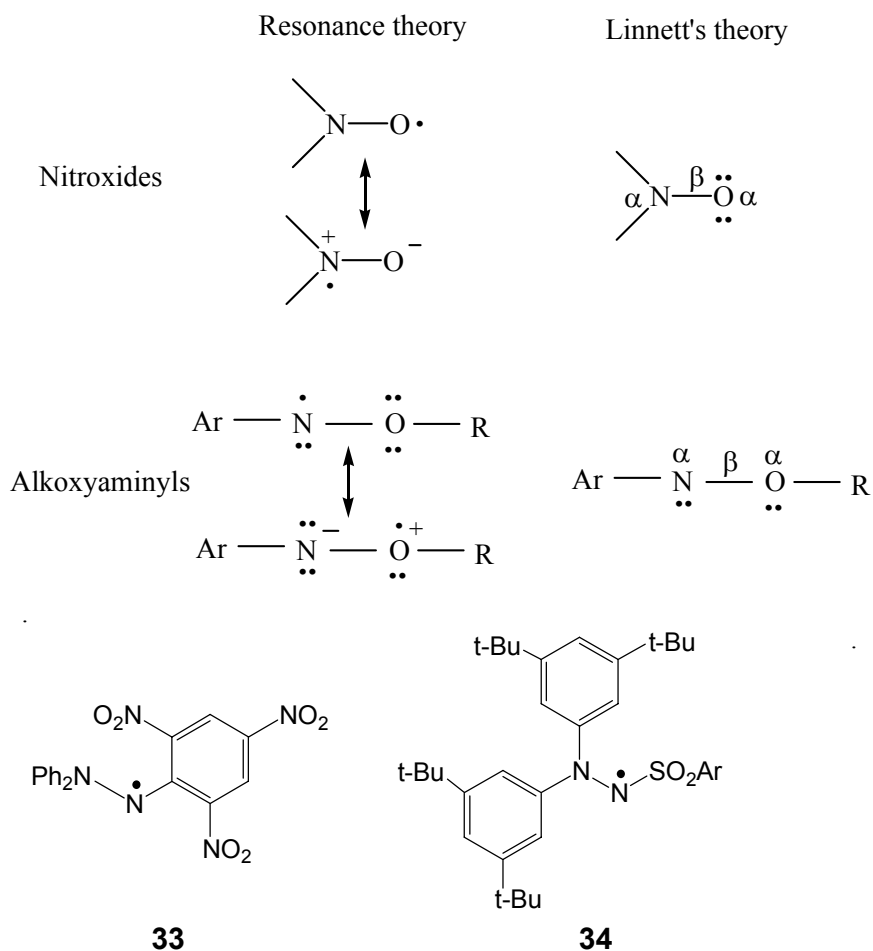
In IFA, Roumanian-made spectrometers for electron paramagnetic resonance (EPR, also named electron spin resonance, ESR) had been built in the 1960s, and we were asked to prepare 2,2-diphenyl-1-picrylhydrazyl (DPPH, **33**), the stable standard free radical for ESR spectroscopy. Having done this in collaborations with Drs. Petre T. Frangopol, Maria Frangopol, Ioana Bally, and Nicolae Negoită I started to explore the reasons for its stability by synthesizing analogs that had different steric and/or electronic effects. It became evident that both types of effects were important, and we were the first to prepare other stable diarylaminyls,¹¹⁰

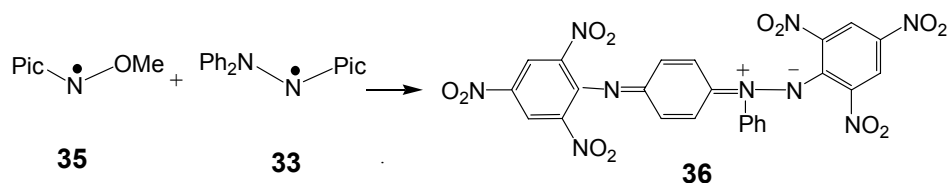
provided that they had an electron-donor and an electron-acceptor group, as well as some steric shielding such as that associated with the picryl substituents with its nitro groups.¹¹¹ I found out that M. J. S. Dewar had already published on this topic,¹¹² and that Linnett had provided a spin-based theoretical explanation for the stability of DPPH and its analogs.¹¹³ Linnett's formulas below explain the stability of nitroxides and alkoxyaminyls, where all atoms have electron octets: the two electronegative atoms share actually 3 electrons (α and β denote opposite electronic spins); the formula for DPPH (**33**) is similar to that of nitroxides, but with O being replaced by N-picryl.

In my publications on aminyls, I named such stable systems "push-pull free radicals". Heinz G. Viehe in Europe¹¹⁴ and Alan R. Katritzky in USA¹¹⁵ advanced later the names "capto-dative free radicals" and "merostabilized free radicals", respectively, and obtained carbon-centered species that are, however, far less stable than their nitrogen-centered counterparts. An interesting side-story concerns my participation in an

international NATO symposium on substituent effects in radical chemistry organized by Heinz Viehe in Louvain-la-Neuve (Belgium) in 1986: Roumania was a member of the Warsaw Pact, and therefore NATO was "the enemy". In my request for obtaining permission to participate with an invited lecture, I had cut off the NATO part of the official invitation letter; I asked the organizers to remove my lecture from the volume,¹¹⁶ and in the list of participants I had included my home address in order not to cause any possible problems to the Bucharest Polytechnic University.

Having obtained hydrazyls **34** with 2,2-diaryl-1-arenesulfonyl substituents as acceptor groups that have far simpler ESR spectra than picrylhydrazyls, it was possible to observe that at room temperature the two aryl groups are non-equivalent, with a rotation barrier around the N–N bond of about 7 kcal/mol.¹¹⁷ This barrier indicates a higher bond order for the N–N, in agreement with the Linnett theory for hydrazyl free radicals.¹¹³





The intense purple color of DPPH is useful for colorimetric follow-up of various redox reactions. One such reaction involves radicals or radical-anions originating from O_2 or H_2O_2 which cause oxidative stress. With Dr. Titus Constantinescu and his coworkers, we also studied spectrophotometrically the reaction between DPPH and the HO free radical generated thermally (from potassium hydroxide in the presence of crown ether 18C6) or photochemically (from salicylaldoxime or from *ortho*-hydroxy-acetophenone-oxime), and we confirmed that one of the two phenyl rings undergoes either *para*-hydroxylation or *para*-nitration via ipso-substitution.¹¹⁸ The *para*-hydroxy DPPH derivative may be oxidized to a quinonoid betainic compound.

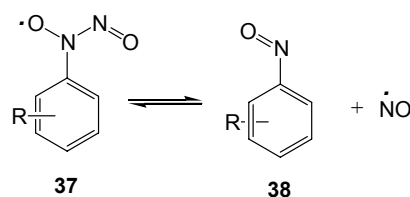
The persistent free radical N-methoxypicrylaminy (35) was prepared by oxidizing N-methoxypicramide with PbO_2 or $Pb(OAc)_4$ in collaboration with professor Robert I. Walter (USA) as well as Drs. Gabriela Stănciuc, Titus Constantinescu, and coworkers; its ESR spectrum were reported.¹¹⁹ When the picryl group was replaced by 2,4-dinitrophenyl, a disproportionation and self-nitration of the free radical were observed yielding picrylaminy derivatives, and the results were confirmed by ^{15}N -labeling.¹²⁰ An interesting reaction was observed when combining N-methoxypicrylaminy (35) with DPPH (33): a blue-colored bis-picryl-betainic product (36) was obtained.¹²¹

One can replace nitro groups in DPPH or in the corresponding alkoxyaminy derivatives by other electron-attracting groups such as cyano, trifluoromethyl, carboxamido or carboxy.¹²² The reactions of DPPH with solid $NaCN$,¹²³ solid $NaNO_2$ or $Na^{15}NO_2$ ¹²⁴ or $NaBH_4$ ¹²⁵ or with phenoxide anions¹²⁶ in the presence of 18-crown-6 ether favoring naked anions led to partial replacement of nitro groups or to *para*-substitution of one phenyl group.

13. NITROXIDES AND DONORS OF NITRIC OXIDE

We also synthesized various stable nitroxides, and prepared for the first time by several methods N-nitroso-N-arylnitroxides (37).¹²⁷ These radicals

can be formed easily either by oxidizing cupferron (N-nitroso-N-phenylhydroxylamine) and its derivatives, or by spin trapping of nitric oxide (NO) with nitrosobenzene derivatives (38).¹²⁸ As this last reaction is reversible, one has the possibility of tailoring NO donors by varying the nature of the aryl group in cupferron analogs.¹²⁹ After the discovery that NO is an essential muscle relaxing factor I came back to this topic, and with colleagues from the Texas A&M University at Galveston and from the University of Texas Medical Branch in the same city, we obtained USA-patents on such NO donors.¹³⁰ The observation that *ortho*-substituents in the aryl group of cupferron analogs accelerate the release of NO *in vivo* can be correlated with the crystal structure that shows, in comparison with the unsubstituted cupferron, larger dihedral angles between the NONO group and the *ortho*-substituted aryl (hence a reduced conjugation). Two other USA patents have been recently obtained for (i) solutions of NO in fluorocarbon emulsions,¹³¹ and (ii) a mixture of two gels that release NO on mixing, for topical applications.¹³² The last procedure was tested on animals with excellent results for accelerating the healing of burns; in China and Taiwan the latter patent is applied for cosmetic products.



14. COMPOUNDS DERIVED FROM BENZOFURAZAN

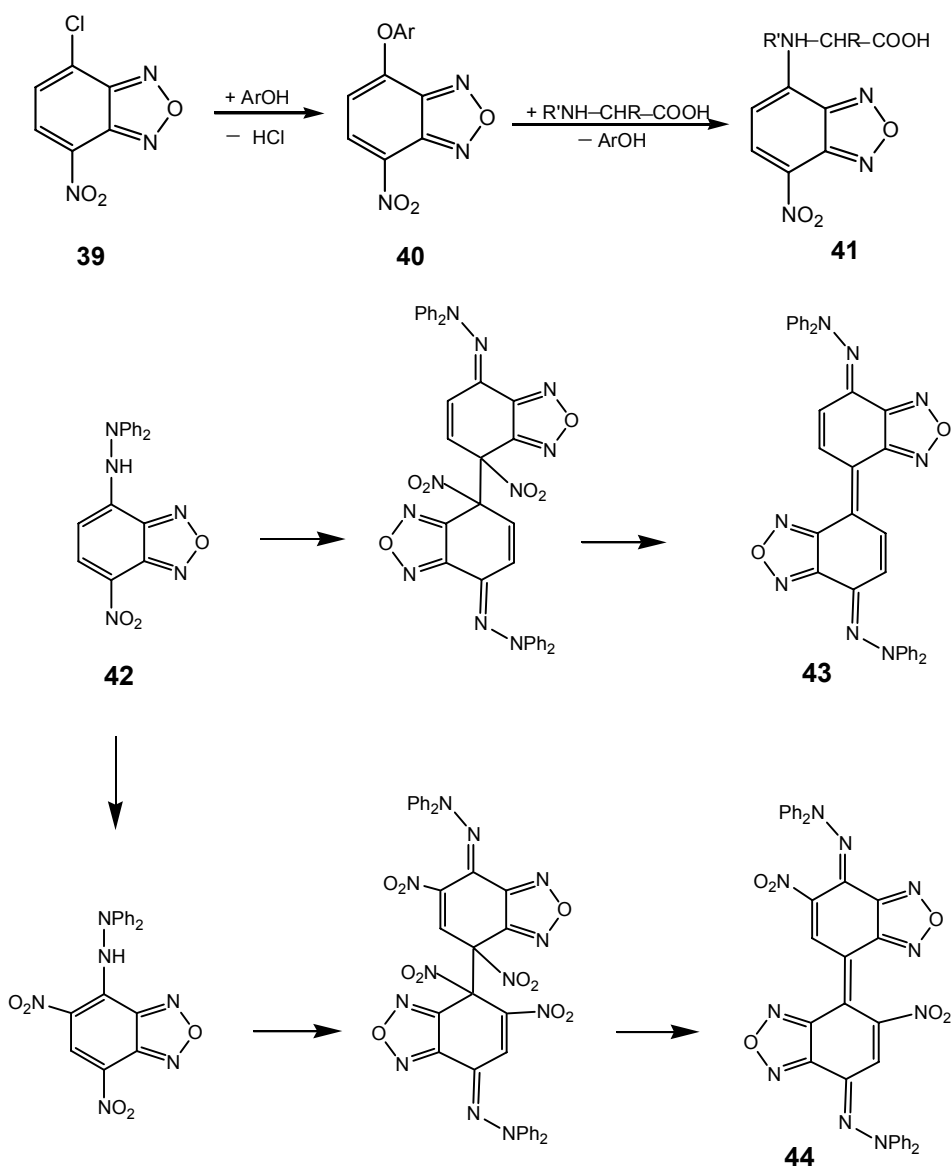
It is no secret that there had been strained relationships between the two most influential Roumanian chemists in the second half of the 20th century: professors Costin D. Nenitzescu (Bucharest Polytechnic) and Ilie G. Murgulescu (Bucharest University). However, during the time I taught at the Bucharest Polytechnic University, I had collaborated with colleagues who had been students of Professor Murgulescu (Victor E. Sahini, Zeno Simon, Mihaela Hillebrand, and Titus Constantinescu) building

bridges between the schools of organic chemistry and physical chemistry. The interest in fluorescence led to collaborations with the last two colleagues involving 2,5-diaryloxazoles¹⁷ and new benzofurazan derivatives, as will be shown in this section.

4-Chloro-7-nitro-benzofuroxan (4-chloro-7-nitro-2,1,3-benzoxadiazole or by its usual abbreviation, NBD-Cl, **39**) undergoes readily nucleophilic aromatic substitutions. Depending on the nucleophile, the substitution product may or may not be fluorescent. On attempting to use amino acids as nucleophiles for attacking NBD-Cl, the reaction failed. However, an indirect route was successful: phenoxides reacted with NBD-Cl affording fluorescent compounds (**40**),¹³³ which have a convenient aroxide leaving group when reacting with amino acids (yielding compounds **41**¹³⁴) or with glucosamine; in the latter reaction

the two glucosaminic anomers could be distinguished by their ¹H-NMR spectra.¹³⁵

The nitro-benzofuroxan moiety is a powerful electron-attracting substituent comparable to a picryl group but unlike the latter it does not provide steric shielding against dimerization. Therefore the substitution product of NBD-Cl with 2,2-diphenyl-1-picrylhydrazine (**42**) does not afford on oxidation a stable free radical because it dimerizes, loses nitric dioxide, and affords a colored quinonoid compound (**43**). A second by-product from this reaction is formed by a parallel process involving homolytic nitration by NO₂, dimerization, and again loss of NO₂ from the dimer affording the dinitro-derivative of the quinonoid compound (**44**). Structures of these reaction products were determined by mass spectra, NMR spectra, and X-ray crystallography.¹³⁶

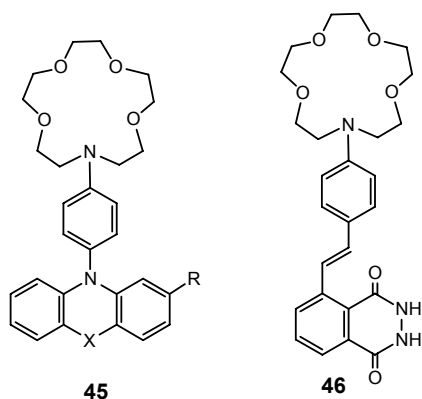


15. COMPOUNDS DERIVED FROM CROWN ETHERS

Dr. Titus Constantinescu has a long-dating interest in thin-layer chromatography and in the synthesis of supramolecular compounds such as crown ethers, and after I moved to Texas I was fortunate to collaborate with him and his coworkers, who share his enthusiasm and dedication. Solid supramolecular complexes of the crown ether 18C6 with the potassium salts of N-methoxypicramide or methoxyamine-3,5-dinitropyridine could be isolated, and used for determining intramolecular rotation barriers.¹³⁷

Aza-crown ethers allow the connection of crown ethers to other groups. Thus, on reacting N-phenyl-aza-15-crown-5 with phenoxazinic or phenothiazinic free radicals, a homolytic aromatic substitution occurs yielding the corresponding azacrown ether connected to the tricyclic aromatic system via a *para*-phenylenediaminic bridge (**45**). On mild oxidation, this bridge loses one electron affording a stable radical-cation analogous to Wurster Blue; ESR spectroscopy and cyclic voltammetry allowed the full characterization of these compounds.¹³⁸

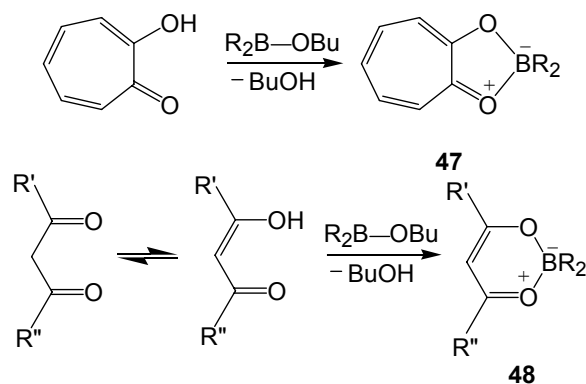
Diazotization of N-phenyl-aza-15-crown-5 followed by coupling with phthalhydrazide resulted in a chromogenic and fluorogenic derivative of luminal (**46**), which can be employed for determining low concentrations of hydrogen peroxide or and of Cu²⁺ ions.¹³⁹



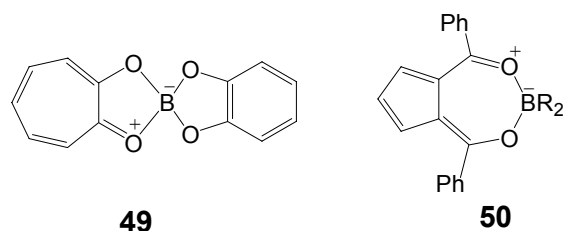
16. BORON-CONTAINING CONJUGATED COMPOUNDS

A systematic approach involving all possible heteroatoms that may be involved in aromatic rings was published in 1959,¹⁴⁰ and it led to the conclusion that boron compounds offered interesting possibilities. Thus we were able to synthesize 5-membered chelate rings including

boron, from tropolone derivatives that benefit from the additional stability provided by the electronic delocalization of the positive charge on the tropylium ring (**47**). The initial borinic ester may be a diarylboronate ester, or an easily accessible *n*-butoxy-benzodioxaborole obtained from catechol and tri-*n*-butylborate.¹⁴¹ These compounds are related to 6-membered chelate analogs (**48**), with a delocalized positive charge on two equivalent oxygen atoms, formed from 1,3-diketones and borinic acid derivatives.¹⁴² Chelate compounds similar to **48** obtained from *para*-anisyl-phenylborinic esters and 1,3-diketones with different end-groups R' and R'' are chiral, as shown by their ¹H-NMR spectra without or with chiral additives.¹⁴³

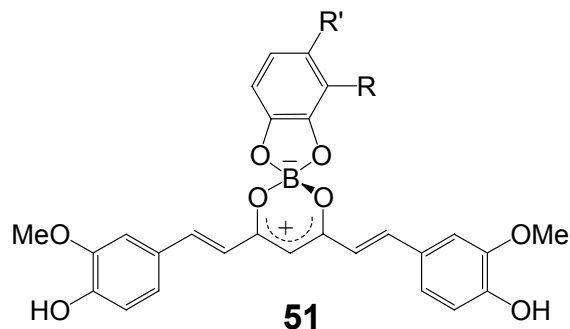


We sent samples of our tropophenylene spiroborates (**49**) to Professor Sutton in England for measuring the anticipated large values of the dipole moments, which were confirmed.¹⁴⁴ A further proof of the electronic delocalization was provided by the large dipole moments of six-membered boron chelates (**48**).¹⁴⁵ In addition to 5- and 6-membered chelate rings involving boron, we also prepared 7-membered chelates (**50**) from borinic acid derivatives and 1,2-dibenzoylcyclopentadiene.¹⁴⁶ The equivalence of the two oxygen atoms in the chelate ring is an essential condition, as attested by the fact that 3-hydroxy-4-pyrones or 3-hydroxy-2-pyrones do not form stable boron chelates.



More recently, in collaboration with professor Cyril Parkanyi, we studied the analogous chelates

(**51**) obtained from curcumin, a compound with remarkable optical and bioactive properties.¹⁴⁷



An analog of pyrylium salts having one of the ring CC bonds replaced by a BO bond was prepared from dibenzoylmethane and a phenylboronic ester;¹⁴⁸ interestingly, it was shown by Nöth¹⁴⁹ that in such 2,4,6-triaryl-1,3,2-dioxaborinium perchlorates there is coordination with participation of a perchlorate oxygen atom. It will be interesting to explore other anions, with lower tendency towards coordination.

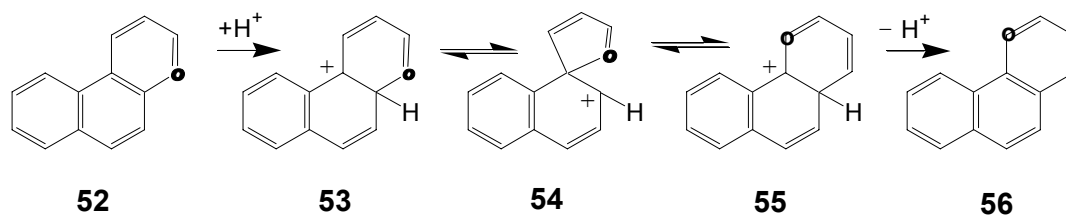
17. AUTOMERIZATIONS OF PHENANTHRENE AND ARSENIC-CONTAINING COMPOUNDS

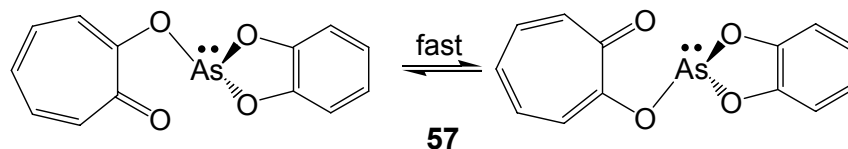
Isomerizations of polycyclic aromatic hydrocarbons (PAHs) in the presence of aluminum chloride had been observed by Buu-Hoï,¹⁵⁰ but the mechanism of this reaction had not been substantiated. The reaction of AlCl_3 with atmospheric moisture is known to afford the superacid HAICl_4 . A sequence of reactions can account for the rearrangement of benz[a]anthracene to chrysene. In the case of isotopically-labeled phenanthrene, the isomerization would become an automerization (degenerate rearrangement), a term we coined for this purpose. By labeling phenanthrene with ^{13}C in position 1 (black circle in the formula **52**), HAICl_4 shifts the label from position 1 to position 4, as shown in a collaboration with Mircea D. Gheorghiu, who is now a professor in USA.¹⁵¹ The reaction sequence is: (i) protonation yielding a stabilized carbocation (**53**) as in all cases of PAHs

with a bay-region; (ii) rearrangement by 1,2-shift leads to **54** with equivalence of positions 1 and 4; (iii) return to the phenanthrene skeleton (**55**) but with reverted positions 1 and 4; (iv) deprotonation affording the automerized product (**56**). In the absence of superacid catalysis, such automerizations of polycyclic aromatic hydrocarbons were shown by L. T. Scott to take place only at temperatures above 1100°C .¹⁵²

An earlier similar experiment carried out with ^{14}C -labeled naphthalene had led us to believe in an analogous automerization for naphthalene, but on repeating the experiment with ^{13}C we could not confirm the previous finding, so that we had to retract the initial claim.¹⁵³

Unlike boron chelates, phosphorus- and arsenic-containing analogs have an unshared electron pair at the central atom, and therefore their chelating tendency ought to be reduced. We prepared a crystalline arsenic analog (**57**)¹⁵⁴ and sent it to Professor Vladimir Minkin at the Rostov-on-Don University, with whom we had earlier collaborations for measuring dipole moments of boron chelates with 1,3-diketones.¹⁴⁵ Crystallographic data of our spiroborates with 5- and 6-membered fully delocalized chelate rings had been obtained earlier.¹⁵⁵ The X-ray diffraction of the 1,3,2-benzodioxarsole ether of tropolone¹⁵⁶ shows unequal As–O bond distances on the side of the 7-membered ring: 1.866 Å to the bonded oxygen, and 2.161 Å to the carbonyl oxygen, whereas on the side of the catechol group the As–O bond distances are 1.819 and 1.879 Å. Also the C–O bond distances differ: 1.360 and 1.372 Å for catechol oxygens and 1.330 Å for the tropolonic oxygen, whereas the C=O bond distance is 1.290 Å. However, an interesting observation was that the ^{13}C -NMR spectra showed rapid valence-tautomerization (degenerate rearrangement) of this compound with no line broadening even at the lowest temperatures that could be reached (-70°C); among other such rapid automerizations for tropolone ethers with 2,4-dinitrophenol or trialkylsilyl groups, our compound bears the crown, with a frequency of arsinyl migration of about 10^5 – 10^6 s^{-1} .





18. MISCELLANEA

On attempting to synthesize fulvenes from cyclopentadiene and benzil (a 1,2-diketone) in the presence of sodium methoxide or potassium hydroxide, an unexpected triphenyl-substituted oxa-pseudoazulene (2,3,7-triphenylcyclopenta [c]pyran, **58**) along with methyl benzoate was obtained. Its structure was determined by X-ray crystallography, and the results were published in collaboration with two other members of the Roumanian Academy, namely professors Mircea D. Banciu and Ionel Haiduc.¹⁵⁷ It will be interesting to attempt analogous reactions of cyclopentadiene involving 1,3- or 1,4-diketones, taking into account that Hafner's azulene synthesis¹⁵⁸ involved 1,5-enediones (pyrylium pseudobases); other interesting related structures would be analogous aza-pseudoazulenes with nitrogen instead of the oxygen heteroatom.

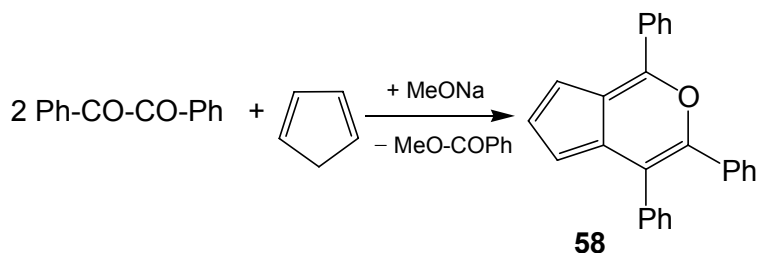
A paper published in Roumanian¹⁵⁹ was about a simple method for obtaining boron trifluoride from calcium fluoride by improving the usual procedure that involves $\text{CaF}_2 + \text{B}_2\text{O}_3 + \text{H}_2\text{SO}_4$ requiring the dehydration of boric acid to obtain the hard, glassy boron oxide which needs to be ground to powder;

it is much simpler to use oleum and boric acid ($\text{CaF}_2 + \text{H}_3\text{BO}_3 + \text{SO}_3$).

For infrared absorption spectra of aqueous solutions, inexpensive cell windows made of large single crystals of elemental sulfur¹⁶⁰ can be useful; such crystals can be easily grown from solutions of sulfur in carbon disulfide.

For organic chemical laboratories that do not possess vacuum equipments, we described a simple technique of evacuating the installation by using the vapor pressure of the solvent.¹⁶¹

To conclude this section, a theoretical prediction of an experimentally observed effect will be mentioned. Reasoning that diatomic molecules that are isoelectronic with dinitrogen possess a considerable stability, my prediction that the O_2^{2+} dication may be a bonded state was confirmed by Dr. Seymour Meyerson using the approach that I had proposed,¹⁶² namely the mass spectrum of $^{16}\text{O}^{17}\text{O}$.¹⁶³ On the other hand, the same question about the ethane dication $\text{C}_2\text{H}_6^{2+}$ led to a collaboration with Pople and Schleyer.¹⁶⁴ we found that the most stable calculated state does not have diborane geometry, but instead has a carbenium-carbonium structure, $\text{H}_2\text{C}^+ - \text{CH}_4^+$.



19. CONCLUSIONS

Looking back at the seven decades since I fell in love with chemistry, I cannot but feel grateful for all the blessings that I enjoyed, starting with my parents and continuing with my teachers, my wife during 57 years, my two children, my collaborators in Roumania and abroad. Although time- and place-circumstances could be viewed as unfavorable – World War II was followed by terrible economic and political situations – I tend prefer a “Pollyanna philosophy” and think myself as someone who was lucky by making the best of

the given cards. Being born in a small country I enjoyed learning French, English, German, and Russian. I was fortunate to have had a splendid teacher in Nenitzescu, to prove worthy of being elected in the Roumanian Academy at an early age, and to have had the opportunities of training as a radiochemist with the effects of working in the IAEA and gathering a small group of young coworkers in IFA. In this organic-chemical laboratory, after synthesizing the chemicals needed by physicists for scintillators or stable free radicals for ESR spectrometry, I tried to look outside the box and improve the known approaches, arriving at

a new synthesis of 2,5-diaryloxazoles or push-pull stable aminyls, respectively. Boron compounds were also relevant in IFA within the context of boron neutron capture therapy.

On embarking in a career for teaching and research in chemistry, I learned to fight against three handicaps due to lack of funds for (1) chemicals, (2) modern equipment, and (3) documentation: lengthy syntheses starting from simple materials took care of the 1st handicap; sending abroad our newly synthesized compounds and publishing results in collaboration allowed not only to circumvent the 2nd handicap, but also to create friendships; these friendships could partly alleviate the 3rd handicap, when chemist friends abroad were kindly sending me books or articles that our libraries did not have.

Usually, eminent Roumanian chemists belonging to previous generations were most often heading university chairs or research institutes, having numerous subordinates as coworkers. By contrast, my coworkers and Ph. D. students came to me because they were choosing to work with me. Also, in contrast to previous-generation chemists who often were engaged in priority controversies defending their "turf", I never had such fights because I liked to share research results and to collaborate both with Roumanian and foreign chemists. The friendly relationships with generous foreign chemists allowed me to obtain from abroad milk powder for my recently-born granddaughter during the weeks after the Chernobyl disaster, or a hypotensive medicinal drug for myself from Salo Gronowitz (Sweden) for several years.

True to my promise not to write books in areas opened by other books, I wrote or edited books opening new areas such as pyrylium salts,⁶⁴ alkene metathesis (a field where our experimental contribution was rather small),¹⁰⁶ chemical applications of graph theory,¹⁶⁵ valence isomers of annulenes,¹⁶⁶ topological indices,¹⁶⁷ chemical topology.¹⁶⁸ With Mircea Banciu, I published a biography of Professor Nenitzescu.¹⁶⁹

The chemists from abroad with whom I collaborated are too numerous to be cited here but I would like to mention a few names: Alan Katritzky, Percy Praill, Paul Schleyer, Roald Hoffmann, Vladimir Minkin, Genadii Dorofenko, Werner Schroth, Christian Roussel, Jacques Metzger, Milan Randić, Sven Cyvin, Danail Bonchev, Ovanes Mekenyan, Douglas Klein,

William Seitz. Also, a few foreign friends with whom I did not co-author publications should be mentioned: Jacques Reisse, Heinz Viehe, Klaus Hafner, Oskar Polansky, Pierre Laszlo, George Olah, Istvan Hargittai, Tibor Braun, Michel Simalty.

I am grateful to my collaborators who, together with me, allowed the areas of stable push-pull aminyl free radicals or of automerization reactions to be associated with my name as shown in Nickon and Silversmith's book *Organic Chemistry: The Name Game*.¹⁷⁰ I am also grateful to the graph-theorists who proved my conjectures about the 10-cage and the unique 11-cage, known as *Balaban cages*. In turn, I hope that my efforts to spread the interest in chemistry and to contribute to the continuously growing edifice of science had a positive influence on my students and research associates.

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