

ADVANCES IN ORGANIC, BIOORGANIC AND NATURAL PRODUCTS CHEMISTRY IN THE INSTITUTE OF CHEMISTRY OF THE ACADEMY OF SCIENCES OF MOLDOVA

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Abstract: This overview deals with the advances in the investigation in the field of organic, bioorganic and natural products chemistry as well as the biologically active compounds in the Institute of Chemistry of the Academy of Sciences of Moldova.

Keywords: organic and bioorganic chemistry, natural products, biologically active substances.

Research in the field of organic and bioorganic chemistry started in 1956, in the Laboratory of Organic Chemistry of the Chemistry Section of the Moldovan Branch of the Academy of Sciences of the former USSR, under the guidance of Professor Gh.V. Lazurievshii. In 1957 the above-mentioned section has been reorganized into two separate ones: of organic and inorganic chemistry. The Institute of Chemistry of the Moldovan Branch of the Academy of Sciences of the USSR has been founded on 15 April 1959, at the same time the section of organic chemistry being transformed into the Laboratory of Chemistry of Natural Compounds. The activity of the newly formed laboratory was focused both on the study of vegetal resources of the republic, and of natural and synthetic organic biologically active compounds. The investigation of two classes of natural organic compounds: alkaloids and terpenoids constituted the main orientation of research at that time. This chemical study has been performed on a large number of spontaneous and cultivated plants, as well as on wastes remaining on the processing of vegetal raw material, both of theoretic and practical value. Over 750 species of local plants were tested for alkaloid's presence (almost half of Moldova's flora). As a result, three plants were selected for further studies: periwinkle, meadow-rue and *Parma buirush*. A high content of alkaloids has been found in *Parma buirush* (*Carex brevicollis* D.C.). The discovery of a plant belonging to the *Cyperaceae* family and containing alkaloids, have already represented a great success, as scientists used to consider these plants inadequate as alkaloids sources. The overall extract obtained from *Carex brevicollis* contained 7 alkaloids, three of which were on record, and four being the new ones: brevicollin, brevicarin, dehydrobrevicollin and homobrevicollin. The structure of these alkaloids and the absolute configuration of brevicollin have been established, the synthesis of brevicarin and brevicollin has been performed, as well as their mutual transformations; the biosynthetic pathway for brevicollin has been elucidated and its biological activity has been studied (I.V. Terentieva, P.A. Vember). Brevicollin proved to be an excellent ganglion blocker, possessing also hypotensive activity. It has been introduced onto medicinal practice by the Pharmacologic State Committee of the Ministry of Health of the former USSR. Subsequently, in 1977, brevicollin has been admitted for utilization in the field of veterinary. While studying the alkaloids of *Parma buirush*, the chemistry of indole has been developed. As brevicollin and brevicarin are derivatives of β -carboline, a synthetic investigation on them has led to the elaboration of a new method of synthesis of β -carboline derivatives. (A.A. Semenov, C.I. Kucicova). A series of new bioactive compounds has been obtained by the condensation of indole and its derivatives with dicarbonyl compounds (G.I. Junghietu). Chisinau became the centre of investigation of indole derivatives; four colloquiums dedicated to the chemistry of indole were organized in Chisinau (1963, 1967, 1971, 1975).

Research related to the chemistry of terpenoids started with the study of compounds, isolated from vegetal wastes generated during the distillation of essential oils from clary sage, lavender, mint, etc. A quite accessible compound has been found – sclareol, a diol isolated from the sage *Salvia sclarea* L. It was found that it is present in the plant in a mixture with its epimer at C-13. The method of their isolation has been elaborated, and their derivatives have been obtained. On the basis of sclareol, nitrogen containing derivatives with spasmolytic and bactericidal properties have been synthesized (D.P. Popa).

Special attention was paid to the study of stereochemistry of a series of labdanic diterpenoids. The absolute configuration at the chiral C-13 centre was established for various diterpenoids: sclareol, labdanolic acid, manoyl oxides and their derivatives, for which contradictory data were published. (P.F. Vlad). Similar problems have been overcome in the case of elucidation of the geometrical configuration of labile isomeric dienols, the abienols (12-cis and trans; cis- and trans-neo- and iso-abienols) (P.F. Vlad, A.G. Russo, M.N. Colța). Subsequently, these synthesized compounds were discovered in natural sources, as well.

In 1963 systematic studies started, related to superior terpenoids, isolated from a series of plant species belonging to the *Labiatae*, *Umbeliferae* and *Compositae* families. Over 50 polyfunctional new diterpenic compounds possessing

complex labdanic and clerodanic structures were extracted from these plants and subjected to detailed studies in order to obtain new physiologically active compounds and solve several taxonomic problems (D.P. Popa, A.M. Reinbold, T.M. Orgheian, L.A. Salei). A series of new compounds were isolated from the *Stachys sylvatica* L., belonging to the *Labiatae* family, bearing a complex cauranic structure, which were used for the systematics of this plant family. For this reason, taxa were described from the chemical point of view for the first time (D.P. Popa, G.S. Pasecinic).

Wastes obtained after the distillation of essential oil from lavender were used to isolate triterpenic acids: ursolic and oleanolic, as well as the diterpenoid kaurenic acid. On their basis, a series of nitrogen containing derivatives has been synthesized, as potential biologically active compounds. Several of these compounds were used as the stationary optically active phase during gas-liquid analysis (B.N. Kalyan).

The composition of the commercial odorant product ambroxide has been established, all the steps of its obtaining from sclareol having been optimized. On the basis of the neutral non-saponifiable part of the oxidation product of sclareol with chromic mixture, the odorant compound ketoxide has been obtained and introduced in practice. The acidic part of the oxidation product, which constituted ~45% of its mass and represented a harmful environmental waste, was used to synthesize the odorant product ambrol, and the technology of its preparation has been introduced. Also, the method of reduction of norambreinolide to sclaradiol was optimized, using instead of potassium borohydride as reducing agent, the *in situ* obtained lithium borohydride, from potassium borohydride and lithium chloride, in isopropanol. This method has also been introduced into production. Regarding the last stage of production of ambroxide– the dehydration of sclaradiol into ambroxide– two new efficient reagents were proposed: the products of interaction of dimethyl sulfoxide with trimethylsilyl chloride or bromine. As a result, the production of odorant compounds from sclareol became almost wasteless (M.N. Colța, E.A. Vorobieova, N.D. Ungur). The chemical composition of the commercial product ambrial was established (P.F. Vlad). A large number of oxidic odorants with tetrahydrofuranic and tetrahydropiranic decalinic and hydrindanic structures belonging to the norlabdanic series were synthesized (M.N. Colța, N.D. Ungur, A.N. Arîcu). Their study demonstrated that the Ohloff triaxial rule, explaining the presence of ambergris odour in the case of decalinic compounds, did not possess prediction force. A new logico-structural and electron-topological theory was proposed revealing the dependence of amber odour on the structure of compounds. (I.B. Bersuker, A.S. Dimoglo, P.F. Vlad, M.N. Colța). Subsequently, the same approach was used for explanation of the dependence of musk odour on the structure of compounds with this odour. (A.S. Dimoglo, P.F. Vlad, I.B. Bersuker).

On the basis of norambreinolide, a series of derivatives with rearranged carbonic skeleton were synthesized, several of which having a strong amber fragrance (L.A. Zadorojnaia, I.P. Dragalin).

In order to obtain norlabdanic derivatives, which can serve as starting material for drimanic sesquiterpenoids' synthesis, the synthesis of high terpenoids and tobacco aromatizators, the ozonization reactions of a series of labdanoides (sclareol, larixol, neoabienols, 13-epitorulosol, isoabienol and sclareoloxide) were studied in detail. As a result, efficient procedures of obtaining of drimanes, sclareoloxide, norambreinolide and ambreinolide were elaborated (A.N. Arîcu). On the basis of norlabdane and labdane, several dozens of tobacco aromatizing compositions were obtained (M.N. Colța, I.P. Dragalin, G.N. Mironov, A.N. Barbă, A.N. Arîcu, N.D. Ungur, V.N. Kulcički). Many of them were introduced at the Chisinau Tobacco Factory. For elaboration and introducing of this work, P.F. Vlad and M.N. Colța, along with their collaborators from the Chisinau Tobacco Factory were rewarded with the State Prize in the field of Science, techniques and production in 1996.

In 1965 the Laboratory of Chemistry of Natural Compounds started research on triterpenic glycosides, extracted from cultivated plants (sugar beet, bean, sunflower, cucumber), as well as spontaneous plants. The structures of over 30 triterpenic glycosides of oleanolic and echinocystic acids, hederagenine, soya-sapogenin C and cucurbitacin B were established. These glycosides contain 5-7 sugar units in their molecules. For the first time, L-ribose was found amongst the sugar units of glycosides. A fast method of photometrical determination of bitter compounds, cucurbitacins, in cucumbers was elaborated and introduced in practice, being especially appreciated by selectioneers. (V.Z. Cirva, I.P. Dragalin). Subsequently, starting with 1971, the research was also focused on steroidal glycosides, isolated from various plant species. Steroidal glycosides are categorized into furostanolic and spirostanolic. The anticancer activity of these compounds was studied and it was found that only spirostanolic glycosides possess such an activity (P.C. Chintea). As a reward for the obtained results in glycosides studies, acad. G.V. Lazurievshii and Dr.hab. P. Chintea got the State Prize for science, techniques and production.

In 1975 the laboratory of Chemistry of Natural Compounds has been divided into Laboratory of Chemistry of Steroidal Compounds (ruled by Dr. P.L. Ceban) and Laboratory of Chemistry of Isoprenoides (ruled by Dr. D.P. Popa). The Laboratory of Chemistry of Steroidal Compounds continued the research on steroidal glycosides; several dozens of such compounds were identified. It was discovered that spirostanolic glycosides possess a high fungicide activity against phytophagous fungi, which attack plants of the *Solanaceae* family (P.C. Chintea, V. Bobeico, N. Mașcenco, S. Șveț). The Laboratory of Chemistry of Isoprenoides continued the studies of polyfunctional diterpenic compounds with labdanic rearranged structure and of kaurenic compounds, as well as the research of products of oxidative transformation of sclareol.

In 1976, a new restructuration of the organic chemistry department took place and research directions were

changed, the focus being set on solving a series of applied issues, important for the economy of the state. The Laboratory of Chemistry of Steroidal Compounds was reorganized: the group of researchers, involved in the study of steroidal compounds, managed by P.C. Chintea, has been transferred to the Institute of Genetics of our Academy. The remaining researchers joined to the Laboratory of Chemistry of Isoprenoids, thus forming the Laboratory of Chemistry of Essential Oil Plants (managed by P.F. Vlad). The Laboratory of Chemistry of Isoprenoids was reorganized into the Laboratory of Chemistry of plant's growth and development regulators (ruled by Dr. D.P. Popa).

After reorganization of the organic chemistry department in 1977 the investigations were directed to the obtaining of physiologically active compounds, useful for agriculture, production of essential oils, perfumery and food industry.

The pedo-climatic conditions of Republic of Moldova are favourable for cultivation of many aromatic plants. In parallel with the production of common essential oils from clary sage, lavender, fennel and others, botanists investigated the possibility of introducing into culture of the new local ethero-oleaginous spontaneous plants, as well as acclimatization of several plants brought from abroad. This plan could not be carried out without a significant chemical assistance. The Laboratory of Chemistry of Essential Oil Plants studied the qualitative and quantitative chemical composition of essential oils obtained from *Tagetes signata* Bar., *Majorana hortensis* Moenchi, several species of absinth (*Artemisia*): *A. Gmelinii* Web ex Stechm., *A. pontica* L., *A. Alba Turra*, *A. haloleuca* Bieb. ex Bess, *A. balhanorum* Krasch, from *Oryganum heracleoticum* L., *Perilla frutescens* L., from a series of hyssop species (*Hyssopus*): *H. montana*, *H. meretacens*, *H. Aristatus*, *H. canescens* și *H. officinalis*), from *Calamintha* Mill (I.P. Dragalin). The chemical composition of the oil obtained from the Vietnamese medicinal plant *Stahlianthus Companulatus* has been studied (N.D. Ungur, Nguen Van Hung). The method for obtaining the anetol from fennicol was elaborated (I.P. Dragalin). The fermentolysis of monoterpene glycosides obtained from rose plants was studied, and on the basis of this research a new fermentation method was elaborated for obtaining rose oil (P.L. Ceban, A.G. Russo, I.P. Dragalin). A new procedure of sclareol isolation from clary sage concrete was elaborated (M.N. Colța, G.N. Mironov), as well as of isolation of 13-episclareol from its natural mixture with sclareol (P.F. Vlad).

Research in the frames of Laboratory of Chemistry of plant's growth and development regulators was focused on obtaining the new biologically active compounds, which would contribute to the fortification of the adaptation potential of cultivated plants and increase their resistance towards harmful environmental factors. A special attention was directed to analogues of natural phytohormones and their synergists, the most efficient and harmless compounds. Perspective preparations were obtained on the basis of succinic and phtalic acids, terpenic retardants were synthesized, as well as kaurenic derivatives with gibberrillinic activity. A large number of analogues of abscisic acid, a phytohormone regulating various processes of plants development, were obtained. The synthesis of this hormone from ionone has been optimized. Alilcyclic, aromatic and heterocyclic analogues of abscisic acid were obtained as well. It was established that many of them exhibit a high activity as plants growth regulators and are of practical importance. (D.P. Popa, A.M. Reinbold, C.I. Cucicova, G.S. Pasecinic).

In 1991, the Laboratories of Chemistry of Plant's Growth and Development Regulators and Chemistry of Essential Oil Plants have joined into one research unit – the Laboratory of Chemistry of Terpenoids (under the leadership of P.F. Vlad). At present, the research of this lab is directed towards the synthesis of labdanic, norlabdanic and drimanic compounds and the electrophilic cyclization of aliphatic and partially cyclized terpenic derivatives by superacid.

In the field of drimanic sesquiterpenoids, the following compounds were synthesized: drim-7-en-11-ol and its acetate, drim-9(11)-en-8 α - and 8 β -ols, driman-8 α ,11-diol, drim-7-en-9 α ,11-diol, drim-7-en-11,12-diol, drim-8-en-7-one, isodrimenine, drim-8-en-11,12-diol-7-one, 6 α -acetoxy-drim-8(12),9(11)-diene and related compounds with ketonic groups in the C-6 position (M.N. Colța, C.I. Kucikova, E. Gorincioi, A.N. Arîcu, A.Gh. Ciocîrlan). Drim-8-en-11-oic and drim-8 α -acetoxy-11-oic acids were obtained as well (G.N. Mironov). Recently, a group of drimanic diols and tetraols were prepared from drim-7,9(11)-diene (P.F. Vlad, A.Gh. Ciocîrlan, M.N. Colța). At present, the syntheses of nitrogen containing drimanes are performed (P.F. Vlad, C.I. Kucikova, A.N. Arîcu).

The second direction of research deals with the study of electrophilic cyclization of terpenoids. Tetracycloeicozanic compounds with a new carbonic structure were obtained on treatment of labdanoids with conventional acids (P.F. Vlad, M.N. Colța, N.D. Ungur).

Systematic studies were performed in the field of terpene cyclizations with superacids. It was established that labdanic compounds on superacidic treatment give tricyclic isoagatonic diterpenes in high yields. Natural compounds of spongian series were synthesized. The reaction of superacidic cyclization of alcohols, their acetates, of acids and their esters of C₁₀-C₂₅ series was studied and it was found that the reaction is chemo- and structural-selective and stereospecific and gives cyclic compounds in high yields. The same regularities of the superacidic cyclization reaction were observed in the case of homo- and bishomo- terpenic derivatives. (P.F. Vlad, N.D. Ungur, Nguen van Hung, Nguen van Tuen, V.B. Perutki).

The utilization of this reaction in the sesterterpene C₂₅ series led to tetracyclic scalaranic compounds obtained from aliphatic terpenoids in one step in high yield, with the formation of a record number of 8 asymmetric centres.

Significant results were obtained on the interaction of sesterterpene and diterpene α,ω -bifunctionalized compounds with the superacid. In this case, the cyclization is initiated by the protonation of the internal double bond,

giving cyclic derivatives containing an isoprene unit in the gem-dimethyl position. This reaction allowed us to perform the biomimetic synthesis of sacculatanic diterpenoids, difficult to obtain in other ways. Interesting results were obtained on the cyclization of terpenylphenylsulfones. When the phenylsulfonic group is situated in the middle of the sesterterpene aliphatic chain, the superacidic cyclization afforded mixtures of scalaranic, heilantanic and rearranged heilantanic compounds (P.F. Vlad, N.D. Ungur, V.N. Kulciti, M. Grinco).

In 1959, in the Laboratory of Chemistry of Natural Compounds, a group of researchers was formed, which performed the synthesis of organic compounds. In 1962, this research group was transformed into the Laboratory of Organic Synthesis (ruled by Dr. A.A. Şamşurin). The investigations were oriented towards the synthesis of bioactive compounds with antibacterial, antiviral, antifungal, antihelmintic activity, preservatives for winemaking and veterinary. This was one of the leading laboratories in the former USSR regarding the synthesis and utilization of pheromones for plants protection from pests.

The isolation, characterization and synthesis of the following attractants have been realized: disparliur (forest pests *Porthetria dispar*), propiliur (white American butterfly *Hyphantria cunea*), ghipliur (queen-bee *Apis mellifera* L.), (B.G. Covaleov, M.A. Rehter, L.A. Vlad, N.P. Dormidontova, R.N. Vascan, E.M. Alitmark).

Related to these syntheses, interesting results were obtained in the field of keto-aldehydes. Syntheses of cumarines were carried out, in order to obtain phytoestrogenic compounds. A new synthesis of cumestrol and its derivatives was elaborated, including the stimulator used in the field of veterinary - *STIMOL-410* (A.A. Samsurin, M.Z. Krimer, L.L. Simonova, V.I. Spector, L.P. Sineavskaia, O.M. Radul). A new method of synthesis of pyrocarbonic acid esters was performed, used as a stabilizers for semi-sweet wines. The products of their transformation were studied as well (A.A. Samsurin, O.E. Crivoşecova, L.V. Curtev). Research related to compounds with juvenile activity was performed. It started with the synthesis of juvenoids known as the "Low mixture" and farnesilic acid derivatives (1968). New diastereospecific syntheses of active compounds and natural juvenile hormones I-III were elaborated. The bioactivity of the synthesized compounds was studied, as well as its dependence on compound's structure. Interesting data were obtained on testing the activity of several juvenile compounds against the Colorado beetle (M.Z. Krimer). Contrary to the existent data, it was demonstrated that compound 1-(4-fluorophenoxy)-7-metoxy-3,7-dimethyl-2E-octen (*PREPARATION AC-1*) induces the sterilization of this beetle (M.Z. Krimer, V.I. Spector, L.L. Simonova).

In 1976, the laboratory of Organic Synthesis was transformed into the laboratory of Chemistry of Preservation compounds (managed by Dr. G.I. Junghietu). The synthesis and investigation of nitrogen-containing heterocycles were started. Investigations related to compounds with preserving properties for fruits, juices, beer, essential oils, and animal food were carried out. For these purposes, the hydroxamic acids were studied, as well as quinoline derivatives and mixed anhydrides of several acids (L.A. Vlad, N.P. Dormidontova). Preservatives for rose petals and fish spawn were proposed (E.P. Stîngaci). As an active preservative for refreshing drinks - *JUGLONE* was proposed (L.A. Vlad). Studies in the field of indole derivatives, isatine and quinoline were carried out. Compounds with antioxidant properties, antiviral and psychotropic properties, useful for medicine were obtained. One of the most efficient compounds was found to be *KETYSAL* – an indole derivative (G.I. Junghietu, E.P. Stîngaci, M.A. Rehter, O.M. Radul). New methods were elaborated for the synthesis of 1,2-dihydroquinolin-4-carboxylic acids, perspective compounds with antioxidant properties for protection of winery materials and preservation of animal gametes.

In 1983 Dr. M.Z. Krimer became the head of this laboratory. In 1985, on the basis of the Laboratory of Chemistry of Preservation compounds the Laboratory Chemistry of Pesticides was created (ruled by Dr. M.Z. Krimer) and a new research direction was chosen: elaboration of new compounds for plants protection and new methods for their production. The main research direction becomes the synthesis and study of 1,2,4-triazole derivatives. New methods for the synthesis of N-alkyl derivatives of 1,2,4-triazole, 1,4-diones, *t*-butylmethylketones were elaborated and the conditions of their selective obtaining were ascertained. A new rearrangement of the triazolyl methyl ketones enolacetates was discovered (E.P. Stîngaci, M.A. Rehter, O.M. Radul).

In 1991 the laboratory returns to its original name – Laboratory of Organic Synthesis.

The synthetic method and technology for obtaining the systemic fungicide tilt (*PROPICONAZOL*) were elaborated, as well as its structural components: 2,4-dichloroacetophenone, 1,2-pentandiol and 1,2,4-triazol, and the alkylation reaction of 1,2,4-triazols (M.Z. Krimer, G.V. Roitburd, I.B. Kalyan, S.I. Pogrebnoi). A series of hydroxyl-derivatives of 1,2,4-triazols were synthesized (E.P. Stîngaci). Investigations were carried out in order to obtain azols and amides of several aliphatic acids (F.G. Shepeli, M.Z. Krimer, F.Z. Macaev). Novel methods were elaborated for the preparation of cyclohexanolic and cyclopentanolic derivatives, which contain nitrones and ketoximes structural fragments (F.Z. Macaev, I.B. Kalyan).

In 1999 Head of Laboratory of Organic Synthesis becomes Dr. hab. F.Z. Macaev. The main research direction was the synthesis of heteroatomic alkyl, aryl and heteryl aliphatic and cyclic compounds.

Starting from acetophenones, benzoic and salicylic acids, syntheses of five-member heterocycles, contained 1,2,4-triazol, oxadiazol, pyrazol, thiazol, and 1,3-dioxolan fragments, were performed. Initial acetophenones were transformed to corresponding phenacyl bromides, 1,3 –dioxolanes, 2-bromomethyl-2-phenyl-1,3-dioxolanes, and chalkones. It was shown that ketalization of phenacyl bromides gives higher yields of 2-bromomethyl-2-phenyl-1,3-

dioxolanes then bromination of 2-methyl-2-phenyl-1,3-dioxolanes (F.Z. Macaev, S.I. Pogrebnoi, E.P. Stîngaci, L.A. Vlad).

Reaction of phenacyl bromides with benzalguanidine was investigated, and it was shown that the nature of reaction products depends on the ratio of initial reagent: when the ration is equimolar, derivatives of 1,2-diamino-4-phenylimidazole were obtained; using of two equivalents of phenacyl bromide leads to derivatives of imidazo-[1,2 α]-imidazole (F.Z. Macaev, S.I. Pogrebnoi, E.P. Stîngaci).

At the first time it was shown that using one-pot reaction it is possible to transform available chalkones to very stable pyrazolines with a high yield. It was shown that derivatives of acetophenones with pyrazolin and oxindol fragments possess an antidepressant activity (F.Z. Macaev, S.I. Pogrebnoi, E.P. Stîngaci, L.A. Vlad, F.G. Shepeli, O.M. Radul). Based on hydrazides of benzoic and salicylic acids, the synthesis of 5-aryl-2-thio-1,3,4-oxadiazoles was performed. A number of synthesized compounds possess a high antituberculosis activity (F.Z. Macaev, S.I. Pogrebnoi, E.P. Stîngaci, L.A. Vlad, G.G. Rusu, A.P. Gudima, Z.Yu. Ribkovskaia).

The syntheses of the natural antifidant cryptomerlone and monoterpene carvone were elaborated for the first time. It has been found that effective method for the preparation of common precursor of above compounds is electrochemical anode oxidation of α -pinene (F.Z. Macaev, L.A. Vlad, A.P. Gudima). It was found, that chiral chlorohydrins or quinolines may be selectively obtained from the pinonic acid (F.Z. Macaev, O.M. Radul, A.P. Gudima).

A number of heterocyclic derivatives of 2,2-dimethylcyclobutane, some of which possess the potential *anti*-HIV-1 activity was synthesized (F.Z. Macaev, O.M. Radul, A.P. Gudima). General methods for stereoselective synthesis of optically active biologically active pyretroids and clerodane compounds and of their precursors were developed from (+)-3-carene, and of (-)- and (+)-carvones (F.Z. Macaev, S.I. Pogrebnoi, L.P. Bets). A series of enantiomeric pure derivatives of 2,2-dimethylcyclopropane, cyclohexanones and octalines were prepared in regio- and stereoselective manner. Among heterocyclic analogues of permethrin, perspective compounds were discovered with anti-inflammatory, fungicide, antimicrobial and insecticide properties. A new method for the preparation of clerodane polyfunctional diterpenoids was developed. Stereoselective syntheses of natural biologically active diterpenoids – antifidantes Lupuline C and (-)-dihydroclerodine from (-)-R-carvone was performed. The most important part of the developed method is initial diastereoselective introduction of hexahydro[2,3-*b*]furan fragment on position C-2 of 3-methylcarvone using Mukayma's reaction, and then the selection of conditions for the annulation of cycle A to corresponding octalines with desired stereochemistry at the atom C-10 of clerodane (F.Z. Macaev).

New N-alkyl isatines as well as spirooxindoles were synthesized (F.Z. Macaev, S.I. Pogrebnoi, O.M. Radul, E.P. Stîngaci, N. Sucman).

New functionalized imidazolium salts that can be classified as ionic liquids were synthesized in an attempt to design specific organic solvents. (F.Z. Macaev, E.P. Stîngaci, V. Sargorovschi, L.P. Bets, N.S. Sucman). On the example of (+)-3-Carene, have identified the appropriateness's of Kondacov's reaction and acetoxymethylation using novel imidazolium ionic liquids. (F.Z. Macaev, L.A. Vlad, L.P. Bets, E.P. Stîngaci, V. Sargorovschi).

Among the asymmetric diamides of malonic acid, compounds capable to increase the myocardial contraction capacity were obtained, which induce blood vessels dilatation and significantly enhance the blood circulation. Several of these compounds were accepted in clinical trials and are currently on the way to be introduced into medical practice (F.Z. Macaev, F.G. Sepeli).

It was found that the nanosized catalytic system (\sim 5-6 nm of γ -Fe₂O₃/CuO), works as an efficient organic phase catalyst (\sim 0.02 mol%) in the one-pot three components Biginelli synthesis (F.Z. Macaev, E.P. Stîngaci, V. Sargorovschi).

Previously unknown *P**-mono, *P**-*N*- and *P**-*N**-bidentate phosphite ligands based on carenes and pinenes were found to be successful ligands for the Pd-catalysed allylation of 1,3-diphenylallyl acetate with (Pr)₂NH, (CH₂)₄NH, PhCH₂NH₂, CH₂(CO₂Me)₂ and 4-Me-C₆H₄SO₂Na. Obtained enantioselectivity up to 99% *ee* is the best result among all known optically active phosphites. In the Pd-catalysed deracemization of ethyl (*E*)-1,3-diphenylallyl carbonate, up to 96% enantioselectivity has been achieved. With participation of the novel *P**-chirogenic phosphite-type ligands excellent enantioselectivity was achieved in the Rh-catalysed asymmetric hydrogenation of some α -dehydrocarboxylic acid esters (up to 93-99% *ee*). (F.Z. Macaev, L.A. Vlad, L.P. Bet).

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