THE CHEMISTRY OF PLANT SUBSTANCES IN UZBEKISTAN

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UDC 547

In this review the main scientific advances in the field of the chemistry of plant substances in Uzbekistan are generalized.

The flora of Uzbekistan is rich and diverse and is represented by 4300 species of plants (there are 8000 species in Central Asia). From time immemorial the people have used plants for treating various ailments. The study of the plant world in the East, especially in Central Asia, began in the middle ages, and the work of Abu Rayhan Al-Biruni and Ali Abu Ibn Sina [Avicenna] in this field formed a whole epoch in the history of world science.

In the Republic, broad and purposeful investigations in the field of the chemistry of plant substances — an important division of bioorganic chemistry — began in 1935, when S. Yu. Yunusov isolated two alkaloids — remerine and armepavine — from the plant *Roemeria refracta* and showed their structures.

The organic substances of plants include alkaloids, isoprenoids (sesqui- and diterpenoids, cardiac and triterpene glycosides, ecdysteroids, carbohydrates, proteins, lignins, etc.).

Over 2500 compounds have been isolated from plant materials, more than 1000 being new. Original studies by Uzbekistan scientists in the field of secondary metabolites have brought the chemistry of plant substances up to the world level, have opened up new chapters in the chemistry of heterocyclic compounds and in conformational analysis, and have enabled light to be thrown on the problem of the interrelationship of the structure, function, and biological action of compounds.

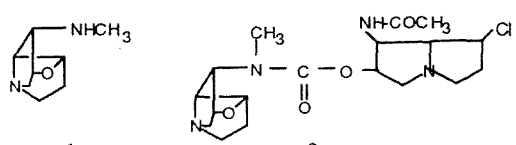
The development of the chemistry of plant substances in Uzbekistan is connected with the activities of two scientific schools — those of Academicians S. Yu. Yunusov and A. S. Sadykov.

A deep chemical study has been made of the alkaloid content of 320 plant species belonging to 33 families. Of these, 292 species from 32 families have been investigated in IKhRV AN RUz and the structures have been determined of more than 540 new compounds belonging to the quinoline, isoquinoline, indole, pyrrolizidine, amaryllis, steroid, quinazolone, sulfur-containing, pyrrolidine, diterpene, and other, classes.

The study of the alkaloids of each plant organ separately over the vegetation periods for different growth sites has revealed common features in the dynamics of the accumulation of alkaloids and their role in plants. These common features have enabled alkaloid-bearing species to be revealed and the maximum amounts of alkaloids to be isolated from the various organs of plants [3, 4] and have also permitted new sources of drugs (galanthamine, scopolamine, atropine, etc.) to be proposed.

New alkaloid-bearing plants of the genera *Nitraria, Diptychocarpus, Haplophyllum*, and others have been found as the result of all-sided chemical investigations [5]; there have been discoveries of plants unique with respect to the number of alkaloids isolated and their structural diversity and unique with respect to the structures of alkaloids having new heterocyclic systems of the following types:

— loline: loline (**1**) and lolidine (**2**) from *Lolium* plants [6, 7]:



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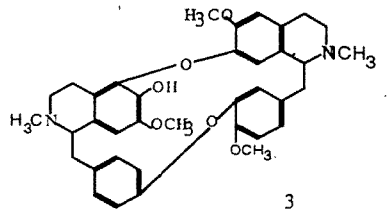
— thalmine: a bisbenzylisoquinoline alkaloid with a 21-membered dioxide ring (**3**) from *Thalictrum*. The discovery of thalmine and the proof of its structure laid the foundation of the new thalmine type of bisbenzylisoquinoline alkaloids [8]:



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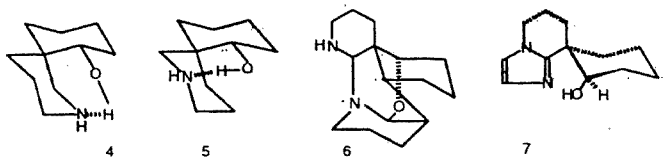
— 2-azaspiroundecane: nitramine (**4**), isonitramine (**5**), nitraramine (**6**), and nitrabirine (**7**) from *Nitraria* [9-11]:



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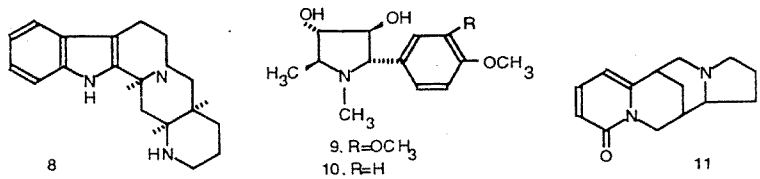
— ethanoazayohimbane: nitrarine (**8**) [12].

Representative of new types of alkaloids have been found:

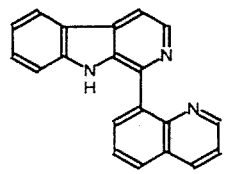
— pyrrolidine series: codonopsine (**9**) and codonopsinine (**10**) from *Codonopsis* [13, 14];

— quinolizidine series: leontidine (**11**) from *Leontice* [15];



8 9. R=OCH$_3$ 10. R=H 11

— β-carboline: komarovine (**12**) [16];



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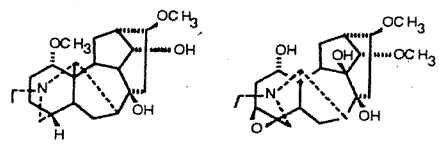
— the diterpene series: aconosine (**13**), excelsine (**14**), dictysine (**15**), coryphidine (**16**), coryphine (**17**), etc [17-23].



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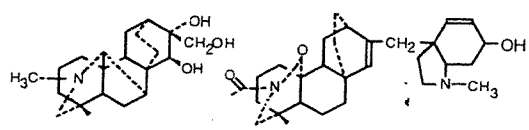

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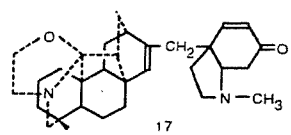

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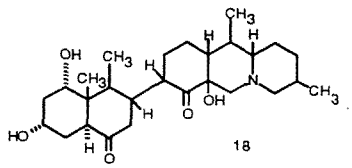
It must be mentioned that the chemical study of the first representatives of the C_{18}-diterpene alkaloids was carried out in Uzbekistan (IKhRV).

An interesting fact is the discovery of the seco-C-nor-D-homosteroid alkaloids, such as severidine (**18**) and also edpetolidinine (**19**) and sevcoridine (**20**) [24, 25].



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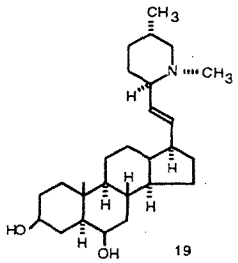

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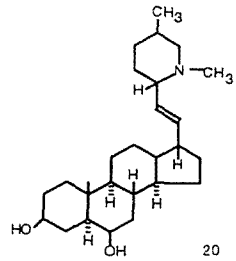

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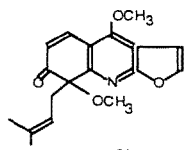
New structural systems have been discovered among the quinoline alkaloids: furanoquinolines with gem-substituted cyclohexadiene rings — perfamine (**21**) and furano-5,6,7,8-tetrahydroquinoline; haplophyllidine (**22**); dimers with cyclobutane rings — haplodimerine ,[26-29]; etc.



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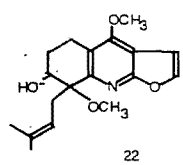

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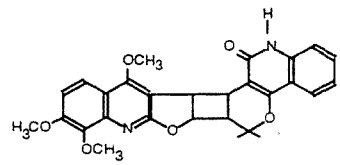

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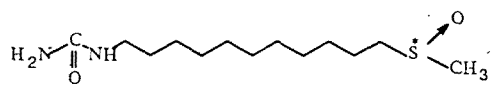
A new class of optically active sulfur-containing alkaloids exhibiting pronounced biological activity and based on a structural chain linking with one another thiomethyl, sulfoxide, and nitryl groupings with *N*-alkylureas in various combinations has been detected in plants for the first time. Diptamine (**24**), diptocarpidine (**25**) and some other alkaloids have unique structures [30, 31].



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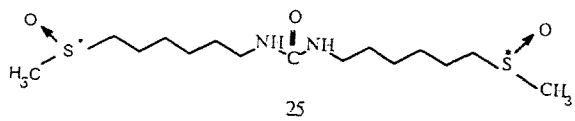

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Dimeric alkaloids of the tropane series have been discovered in plants of the Convolvulaceae family for the first time.

As a result of pharmacological studies of the alkaloids isolated, compounds have been revealed that possess antiarrhythmic, local anesthetic, spasmolytic, antiphlogistic, gangliolytic, curare-mimetic, psychostimulating, arrhythmogenic, cholagogic, antihistamine, sedative, tranquilizing, estrogenic, bronchodilating, and other, properties.

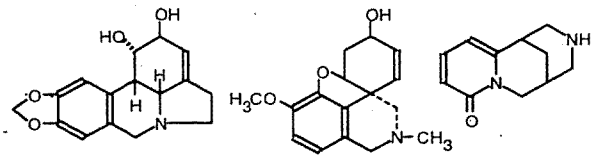
Antiarrhythmic properties were first detected in a number of diterpene alkaloids. These studies form a new direction in the creation of antiarrhythmic drugs.

Original alkaloids with an aphrodisiac action have been found. Work on the creation of drugs with an aphrodisiac action is opening up a new direction in the study of steroid alkaloids [32].

Structure—activity relationships have been determined on the basis of the structures determined for alkaloids and the results of pharmacological trials for a whole series of alkaloids and their derivatives, and the structural elements responsible for definite types of activity have been found. The performance of mutual transitions of alkaloids has shown interrelationships between substances of a given species, genus, and family of plants.

Starting from the results of a study of the dependence of their pharmacological properties on the structures of alkaloids, approaches have been found to the directed synthesis of valuable drugs from readily available substances.

Fundamental investigations in the field of alkaloids have served as an impetus to the development of large-scale studies on the practical utilization of plant resources and the creation from them of highly effective medicinal preparations, among which lycorine (**26**), galanthamine (**27**), cytisine (**28**), deoxypeganine (**29**), and allapinin (**30**) have ben introduced into medical practice.



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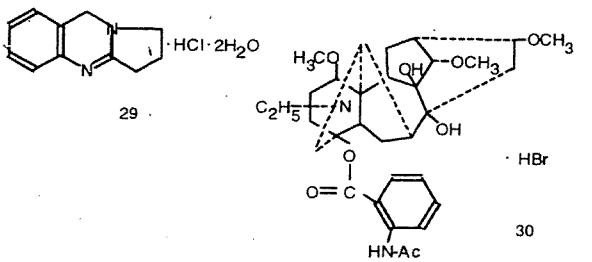
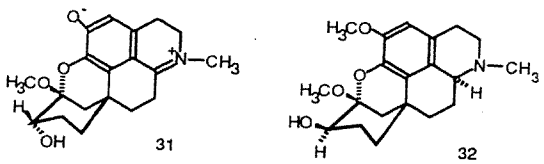


29 30

More than 120 bioreagents have been created and realised for medico-biological investigations; these include bicuculline, aconitine, heliotrine, imperialine, and others [32].

More than 20 species of plants from five families have been studied in the chemical faculty of Tashkent University and about 70 alkaloids, of which 50 were new, have been isolated from them. N-Oxides of homoaporphine and of homoproaporphine alkaloids, quaternary dehydrohomoaporphine alkaloids such as regecoline (**31**), and tetrahydro-7-oxohomoproaporphine alkaloids such as regelinone (**32**), and others, have been isolated for the first time. The tropolone alkaloid speciosamine (**33**) has an unusual structure [33-35].



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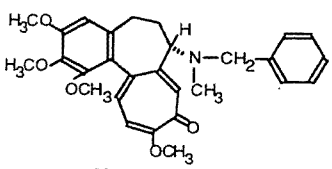

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The results of an investigation of the stereochemistry of alkaloids of the matrine series have permitted a broadening of certain fundamental principles of conformational analysis.

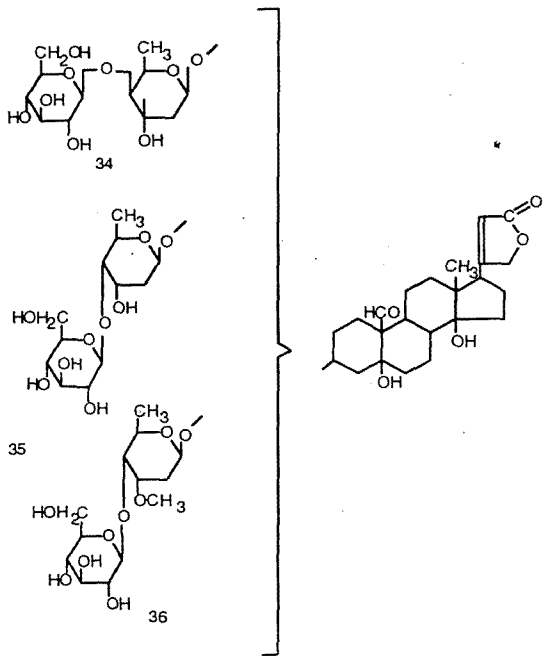
Using experience of work with tropolone alkaloids, a procedure for the stagewise control of production and new methods for obtaining the anticancer drugs colchamine and colchicine from a *Colchicum* plant have been developed [36].

The biosynthesis of alkaloids from plants of the Fabaceae (Leguminosae) family has been studied for the first time, and it has been shown that the quinolizidine and piperidine alkaloids are formed from lysine [37].

Isolated studies on alkaloids have been conducted in the Tashkent Pharmaceutical Institute: the alkaloids of nine species of plants in the Lamiaceae (Labiatae) family have been investigated, and the alkaloid stachydrine has been isolated [38].

A chemical study of isoprenoids in Uzbekistan began in IKhRV at the end of the 50's. A total of 270 compounds have been isolated and the structures of 190 new ones have been shown.

Great advances have been achieved in the field of the chemistry of cardiac glycosides. Pioneering studies to establish the structures of the cardiac glycosides olitoriside (**34**), isolated from the seeds of jute, *Colchorus olitorius* [39], and of erysimoside (**35**), isolated from the erysimum *Erysimum diffusum* [40], have opened a new chapter in the chemistry of natural compounds in the former Soviet Union.



In its chemical structure and cardiotonic action, olitoriside (**34**) is close to K-strophanthidin-β (**36**) [41]. The drug was approved for medical use in 1960.

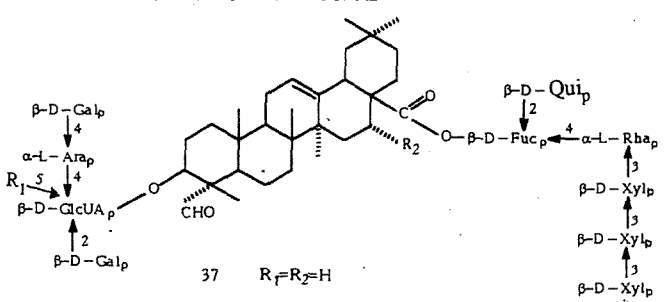
In all, the structures of more than ten cardiac glycosides have been established.

Triterpene glycosides form the basis of the saponins. The most interesting results have been obtained in an investigation of the Turkestan soapwort *Allochruza gypsophiloides*, in which four glycosides were found [42-44].

The immunostimulating preparation allokhrozid (**37-39**), used for the production of an antitumoral vaccine, has been created from the saponins of *Allochruza gypsophiloides* [45].

Considerable attention has been devoted to the glycosides of common licorice, *Glycyrrhiza glabra*, which possess foam-forming properties. A method has been developed for obtaining a foaming agent to be used in the confectionery industry.

ACANTHOPHYLLOSIDE



37 $R_1=R_2=H$

ACANTHOPHYLLOSIDE C

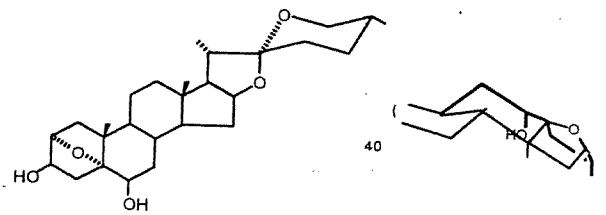
38 $R_1=\beta$-D-Glc, $R_2=H$

ACANTHOPHYLLOSIDE D

39 $R_1=H$ $R_2=OH$

Original investigations have been conducted in the field of steroids of the furostan and spirostan series. This group of plant metabolites possesses a broad spectrum of action and some of its representatives form the starting material for the synthesis of steroid hormones and their analogues.

Many species of onion, *Allium*, have been studied for the presence of furostan and spirostan steroids, and rarely encountered metabolites such as anzurogenin B (**40**) have been isolated [47].



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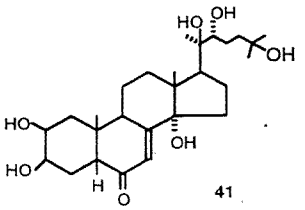
Particular mention must be made of work on the ecdysteroids — compounds regulating the most important vital functions of both animal and plant organisms. It has recently been shown that ecdysteroids are widely distributed in the plant world [48, 49]. Of the 53 phytoecdyteroids isolated, 37 proved to be new.

In the traditional medicines of various countries, plants of the genera *Silene*, *Rhaponticum*, and *Ajuga* are used in cases of overstrain, loss of appetite, weakening of the reparative functions of the organism, etc. As has been shown, this property is due to the presence of ecdysteroids, mainly ecdysterone [50-52]. The drug ekdisten, with a tonic action (**41**) is based on ecdysterone isolated from *Rhaponticum carthamoides* and has been put into production.



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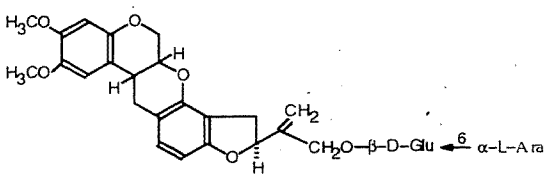
A study of the plant *Amorpha fruticosa* (fam. Leguminosae) [53] has led to the discovery of a new class of plant glycosides containing rotenone derivatives as aglycons. From one of them — amorphin — the drug glirofam has been created, and this has been approved as an agent for the treatment of atherosclerosis.



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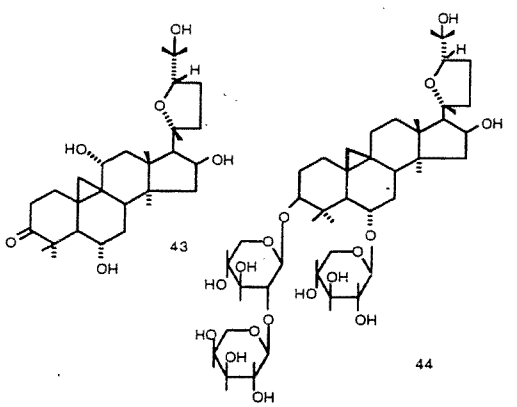
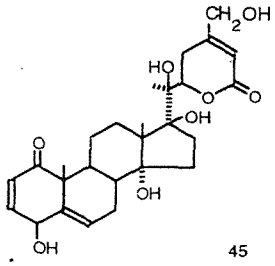
Investigations in the cycloartane series from plants of the genus *Astragalus* have led to the determination of the structures of more than 60 new compounds of genin and glycoside nature (throughout the world there are about 300 of them), representatives of which are cycloasgenin A (**43**) [54] and askendoside D (**44**) [55]. The foundation has been laid for a new direction.



43 44

A peculiar group of C-28 plant steroids is formed by the withasteroids. From plants of the genera *Physalis* and *Datura* [56, 57] 18 withasteroids have been isolated, and the structures of 14 of them have been shown. 28-Hydroxywithaphysanolide (**45**) has a unique structure [58].



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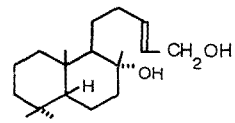

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Some representatives of the withanolides possess antiphlogistic and immunomodulatory activities [59, 60].

Among low-molecular-weight classes of plant compounds, a considerable position is occupied by flavonoids, coumarins, and terpenoids. These substances are combined into two large independent groups — terpenoids and phenylpropanoids, formed by a single biogenetic scheme.

Numerous species have been investigated for the presence of the above-mentioned classes of plant substances and more than 500 have been isolated, including 280 new ones.

The first studies on sesquiterpene lactones were begun in IKhRV AN RUz in 1967. More than 300 species of the plants of Central Asia have been analyzed and the structures of 60 new lactones, including guaianolides, germacranolides, and pseudoguaianolides, and also derivatives of the diterpene clerodane, have been established [61]. Among the compounds isolated have been found substances possessing various types of biological activity.

In the chemical faculty of Tashkent State University, 12 of the 17 species of *Lagochilus* growing in Uzbekistan have been studied for the presence of diterpenoids and more than 30 compounds have been isolated, including 20 new ones [62—66].

A number of new diterpenoid lactones have been detected in plants of the *Lagochilus* genus for the first time. The isolation has been reported of an interesting diterpenoid — vulgarol (**46**), which is a representative of a rarely encountered group of bicyclic diterpenoids with the *cis*-linkage of rings *A/B* [67].

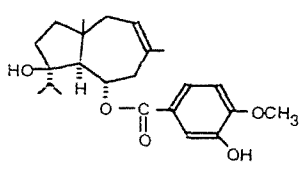
The highly effective hemostatic Lagoden has been created on the basis of the diterpenoid lactone isolated [68].

The terpenoids of 50 species of *Ferula* plants have been studied in IKhRV AN RUz, and more than 250 compounds have been isolated. It has been shown for the first time that the plants of this genus contain, in addition to terpenoid coumarins and sesquiterpene lactones, a new group of natural compounds characteristic for this group — esters of terpenoid alcohols with aromatic and aliphatic acids [69-72].

The structures and stereochemistries of about 100 new terpenoids of the acyclo-, monocyclo-, and bicyclofarnesane, germacrane, guaiane, eudesmane, humulane, carotane, and himachalane types have been established. The terpenoids of the last three types were first isolated from the flora of Uzbekistan. Unique structures relating to the carotane, humulane, and himachalane types of sesquiterpene derivatives, and also to the clerodane diterpenoids and arylnaphthalene lignans, have been revealed.

Two drugs with an estrogenic action are based on *Ferula* terpenoid esters: panoferol (**47** — a mixture of ferutin (A), teferin (B), and ferutinin (C)) for use in poultry farming; and teféstrol (**48** — a mixture of ferutinin (C) and tenuferidin (D)) — the first domestic estrogen based on plant materials for use in obstetric-gynecological practice. Both drugs have been introduced into the national economy.

At the present time, studies are being conducted for the creation from teféstrol of an abortifacient in early periods of pregnancy and the first contraceptive in combination with gestagens.



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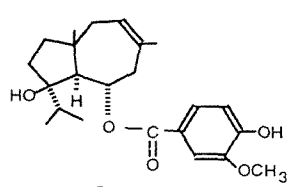

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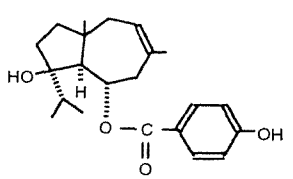

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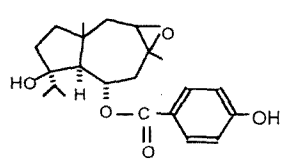
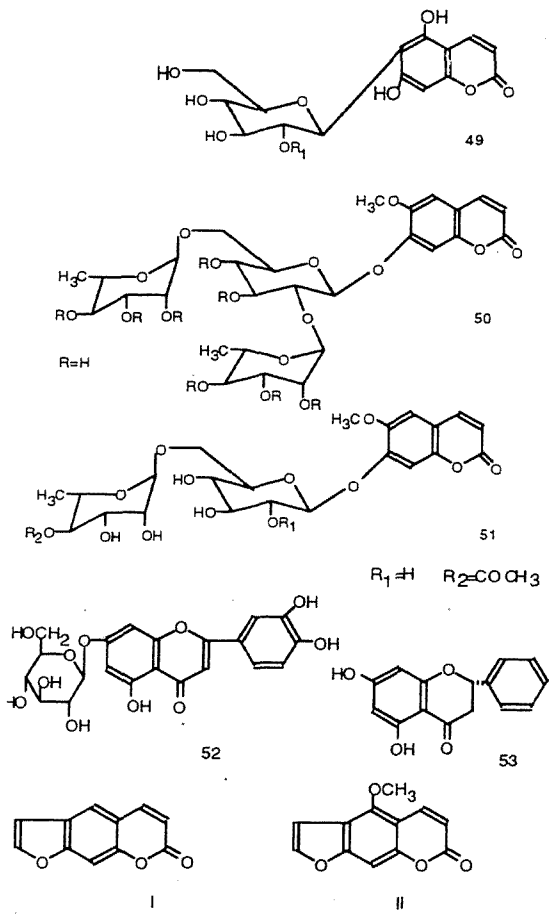


D

By studying the relationship between structure and estrogenic activity in esters of varous *Ferula* species, certain fragments of the molecule attenuating estrogenic activity have been discovered, and methods have been proposed for finding substances with estrogenic activity among esters of terpenoid alcohols.

More than 40 species of plants have been subjected to a complex study of their coumarins, flavonoids, and lignans, and more than 150 substances have been isolated, including 65 flavonoids and 15 coumarins and lignans. The flavonoids include derivatives of flavone, flavonol, flavonone, chalcone, and isoflavone. It has been shown for the first time that plants of the genus *Haplophyllum* contain flavonoids together with other compounds. Acylated phenol glycosides of the coumarin series, flavonoid glycosides, a coumarin C-glycoside, and a coumarin trioside have been found for the first time in this plant. They include the first coumarin C-glycoside — dauroside D (**49**) [73] —, the first trioside of the coumarin series — haploperoside E (**50**) [74]—, and the first acylated phenol glycoside of the coumarin type — haploperoside B (**51**) [75].

Among compounds of this class, substances have been found that possess pronounced hypoazotemic, hypolipidemic, antiatherosclerotic, antiophlogistic, cholagogic, and spasmolytic actions, and such drugs have been created as tsinarozid [cynaroside] (**52**) — a hypoazotemic agent from *Ferula varia* —, pinotsembrin [pinocembrin] (**53**) — an antiphlogistic from *Glycyrrhiza glabra* —, and psoberan (**54**) — a photosensitizing agent from *Ficus carica*.

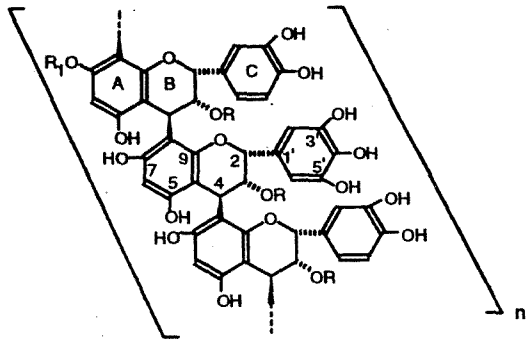


Some of the most widely distributed natural flavonoids are the proanthocyanidins — polymeric derivatives of flavan-3-ols (tanning substances).

A chemical investigation of this class of plant substances in Uzbekistan is being conducted in IKhRV AN RUz, and isolated studies of a nonstructural nature in this field are being carried out in the Institute of Bioorganic Chemistry of the Academy of Sciences of the Republic of Uzbekistan, Tashkent State University, and Tashkent Pharmaceutical Institute.

More than 30 species of plants used in folk and scientific medicine have been studied, and more than 100 compounds have been isolated of which about half were new; the structures of the latter have been established. The proanthocyanidins isolated are polymers and copolymers of (+)-catechin, (−)-epicatechin, (+)-afzelechin, (−)-epiafzelechin, (+)-gallocatechin,

and (−)-epigallocatechin [76-80]. The drug kavergal (**55**), possessing an antihypoxemic action, is based on a proanthocyanidin isolated from the bark of *Quercus robor*.



55

Isolated studies in the field of lipid chemistry, characterizing the lipids of certain seeds in general outlines, had been carried out in Uzbekistan before the setting up of the lipid chemistry laboratory in IKhRV AN RUz (1959). Complex chemical investigations of the lipids of wild, and some cultivated, plants of Central Asia are currently being conducted in IKhRV AN RUz.

The lipids of more than 250 plant species have been characterized, and the structures of more than 60 oxygenated acids and of three halo acids have been shown [81-6].

New types and classes of plant lipids have been discovered; for example, allyl hydroxy fatty acids [82-84], phosphono analogs of phosphatidylethanolamines [87], etc.

The following acids have been detected in higher plants for the first time: *erythro*-9,10-dibromo- and *erythro,erythro*-9,10,12,13-tetrabromostearic acids (from *Eremostachys moluccelloides*) [86], and 12-hydroxyheptadec-9-enoic acid (from *Gossypium hirsutum*) [88]. Information has been obtained for the first time on the fine structure of the autooxidized lipids formed in the alkaline and absorption refining of cottonseed oil [89,90]. Isomeric 18:2 and 20:2 acids, which are unusual for the phospholipids of higher plants, have been found in the seeds of *Erysimum silvestris* [91].

Concentrates of biologically active lipids and lipophilic substances have been created on the basis of the results of an investigation of bioactive lipids from the processing wastes of the agricultural and pharmaceutical industries. Thus, a bioadditive from *Rhaponticum carthamoides* wastes has been used as a component of the children's foaming detergent Limonchik, and new shampoos and an edible cream have been created with a bioadditive from *Aconitum leucostomum* wastes.

More than 160 species of wild and cultivated plants of Central Asia have been investigated for their carbohydrate contents [92-94], and so have the wastes from some fruit, vegetable, and technical crops [95-98]. All the homogeneous fractions of polysaccharides from 30 plant species have been subjected to deep chemical study; more than 30 compounds have been isolated from them, and the primary structures of 25 new ones have been determined as polysaccharides of various types, such as a glucomannan [99-101], a glucogalactan [102], a mannan [103], a glucan, a glucofructan [104-106], a pectin [107], etc. Conclusions have been drawn on the interrelationship between the polysaccharide compositions and taxonomic positions of plants of the genus *Eremus*. A new type of glucofructans, containing both inulin, 1→2 (**56**), and levan, 2→6 (**57**), glycosidic bonds has been found in *Allium* (onion) and *Polygonatum* (Solomon's seal) plants [106, 108].

β-*D*-Fruf2-[6-β-*D*-Fruf2-]$_n$-[-1-β-*D*-Fruf2-]$_n$-β-*D*-Fruf
| |
4 2
| |
2-β-*D*-Fruf 1-α-*D*-Glcp

56

Glcp1->2Fruf1-[>2Fruf1-]$_2$-2Fruf6-[>2Fruf1-]$_3$->2Fruf6-[2Fruf1-]$_2$-
2Fruf6-2Fruf

57

A number of polysaccharides possessing plasma-substituting, antiulcer, hypocholesteremic, cryoconserving, emulsifying, growth-stimulating, and anticoagulant effects have been found [109]-[112].

The preparations érekoll and tsitoflot (from *Eremurus*) are recommended for use in medical practice as analogs of Ficoll, which is used for isolating immunocompetent blood cells.

In the 70's the polysaccharides of the cotton plant were studied in Tashkent State University, and xylans were isolated from this plant for the first time [113].

A deep chemical investigation of plant proteins was begun in IKhRV AN RUz in 1966.

Methods were developed for isolating the cottonplant reserve proteins 7S and 11S globulins, and a number of enzymes possessing proteolytic, malate dehydrogenase, aspartate aminotransferase, lipase, esterase, and phenol oxidase activities, and also protease inhibitors [114-121].

The primary and secondary structures of the 7S and 11S globulins, a cottonplant esterase, and ricin-T from the seeds of the castor-oil plant have been established for the first time [122-124].

The influence of plant-growth regulators on the activity of enzymes has been studied and the results can be used to evaluate the efficacy of plant-growth stimulators [125].

It has been established that during the growth of cotton seeds the 7S and 11S globulins undergo proteolysis by the appropriate proteases [126].

A method of protein markers has been developed for determining the species affiliations of cotton plants and also for differentiating between varieties with the aim of carrying out purposeful selection in the breeding of new varieties of cotton plant with given characteristics [127, 128]. An immunochemical method has been developed for evaluating new wilt-resistant breeding varieties [129].

The toxic proteins and allergens of the seeds of the castor-oil plant have been studied and immunological methods for determining them in the products of the industrial processing of the seeds have been developed [130, 131].

In recent years, work has been begun on the study of the role of protein structure in the formation of systems with given properties and on the conformational mobility of protein molecules when they interact with various classes of substances [132-134].

In Uzbekistan the study of lignin began at the end of the 50's—beginning of the 60's in connection with the necessity of utilizing the hydrolysis lignin obtained in three hydrolysis factories.

The main material for hydrolysis is cottonseed husks. In the Scientific–Research Institute for the Chemistry and Technology of Cotton Cellulose investigations have been conducted on the hydrogenolysis of the native and hydrolysis lignins of cottonseed husks, and about 60% of low-molecular-mass phenolic substances suitable for further organic synthesis have been obtained [135]. Since 1970, investigations of the lignins of annual and perennial herbaceous and cultivated plants have been performed in IKhRV AN RUz.

It has been found that with the growth of the cotton plant the lignin becomes more highly methoxylated [136]; the dioxane lignins of the cotton plant and of kenaf have been fractionated with respect to molecular mass [137]; and a scheme of the structure of an averaged fragment of the molecule of cotton plant dioxane lignin consisting of 18 structural units has been drawn up.

A number of valuable products have been obtained from lignin and its cleavage products. For example, a new catalyst has been proposed for obtaining vanillin in high yield from lignosulfonates [138]; a new organic fertilizer has been obtained by the ammoniation of hydrolysis lignin [139]; and an anticorrosion paint has been obtained from modified hydrolysis lignin.

The principal industrial agricultural crop of Uzbekistan is cotton. For this reason, numerous groups of scientists specializing in various fields are engaged in its all-sided study. The specific pigment of the cotton plant — gossypol, a polyfunctional compound the molecule of which contains six hydroxy groups and two aldehyde groups — is being studied. More than a hundred Schiff bases and a number of drugs have been synthesized from it [140-143]. Interesting results were obtained in a study of the behavior of gossypol in lower alcohols [144, 145].

A special position is occupied by the original work of Academician A. S. Sadykov devoted to a complex chemical study of the cotton plant. More than 100 compounds have been isolated from this plant, including representatives of many classes of organic compounds [146-148]. Investigations of the polyphenols of the cotton plant — flavonols, anthocyans, proanthocyanidins, and gossypol pigments — have proved to be the most fruitful [147].

The results of the investigations have permitted the development of scientific principles for the creation of natural food pigments with various tints from certain plants of the *Malvaceae* family. This work has found practical use, and at the present time the pigments and combinations of them are being used in the food industry and in the production of nonalcoholic beverages [149].

A number of compounds from the cotton plant have been shown to possess a high interferon-inducing, antitumoral, and antiviral, including anti-AIDS, activity. A health-preserving liniment of gossypol (3%) and megosin (3%), and batriden tablets have been created from cotton plant gossypol and introduced into practice.

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