SULFUR-CONTAINING ALKALOIDS

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Among the whole diversity of natural compounds, sulfur-containing substances of plant origin occupy an insignificant place, but in spite of this they excite enormous interest among scientists. An indication of this is given by the international symposia on low-molecular-weight sulfur compounds that are held periodically. In the lectures presented at the symposia it is reported that low-molecular-weight sulfur compounds play an important role in the vital activity of plant and animal cells. A systematic study of the flora by workers in various fields has led to the isolation of various natural substances produced by plants.

Sulfur-containing plant substances do not belong to one class of organic compounds: in addition to thiourea derivatives we find here alkyl sulfides, sulfoxides, and isothiocyanates. Their interrelationship follows immediately from their common presence in a plant. Sulfur is present in plant amino acids, amines, organic acids, some vitamins (vitamin B_1, vitamin H, pantethine, pantetheine, biocytin, biotin *l*-sulfoxide), and antibiotics [penicillin, gliotoxin, thiolutin, acidomycin (mycobacidin), aureothricin].

The role of sulfur in proteins is important. In the majority of proteins sulfur fulfills a structural function, i.e., it participates in the formation and stabilization of their molecular structures.

Sulfur-containing substances are found most frequently in seeds and roots and more rarely in leaves and flowers. They are widely distributed in plants of the family Cruciferae (in approximately 30 species), are found in some species of the families Lilaceae, Capparidaceae, and Leguminosae, and more rarely in representatives of other families [1].

Recently, sulfur-containing bases have also been found in plants, but these are characteristic only of certain families. Among these we may mention the families Rhizophoraceae, Nymphaeaceae, Cruciferae, and Rutaceae.

On considering all the sulfur-containing alkaloids that have so far been isolated from the chemical point of view, it is easy to observe that a definite type of base is characteristic for a given species of plant. Here sulfur does not play a decisive role. If, however, we consider them on the basis of the inclusion of sulfur in the structure, all sulfur-containing bases can be arbitrarily divided into two groups: alkaloids with a sulfur atom in a ring and alkaloids with acyclic sulfur (Table 1). In their turn, the alkaloids included in the first group can be divided into three subgroups: Nuphar alkaloids, peptide alkaloids, and dithiolane derivatives. From the second group we can isolate two subgroups: oxazolidinethione derivatives and derivatives of urea and thiourea.

A new type of sulfur-containing alkaloids in plants of the family Nymphaeaceae was described by Achmatowicz and Bellen in 1962 [2]. In these compounds, the sulfur forms part of a new ring structure. Two species of plants of the genus Nuphar – N. japonica and N. luteum – have been subjected to a systematic chemical study. From the rhizomes of N. luteum growing in Poland, the above-mentioned authors isolated four sulfur-containing bases – thiobinupharidine, allothiobinupharidine, pseudothiobinupharidine, and thiobideoxynupharidine – and two years later they isolated neothiobinupharidine [3-5]. Structural investigations showed that they belong to the sesquiterpenoid or triterpenoid type, combining quinolizidine and furan systems with a tetrahydrothiophene system.

Thionupharoline is a new sulfur-containing alkaloid from N. luteum. The results of a study of spectral characteristics and chemical properties have shown that it is a hydroxy derivative of neothiobinupharidine in which the OH group is present at C-1 or C-2 of one of the two quinolizidine systems [7].

Other sulfur-containing alkaloids of this genus have been described. LaLonde et al. [8] have isolated two isomeric carbinolamines which have been called, 6,6′-dihydroxythionuphlutines A and B, the reduction of which led to the stereoisomeric thionuphlutines A and B. Thionuphlutine A has recently been shown to be identical

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TABLE 1

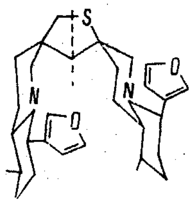
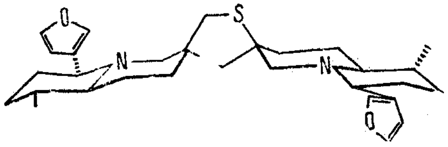
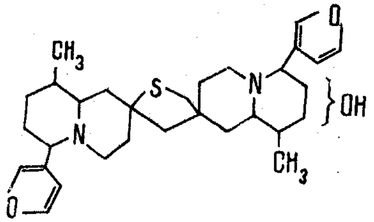
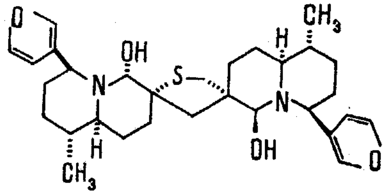
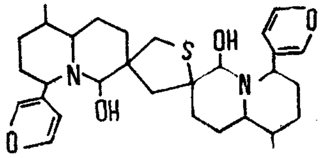
Name and composition of the alkaloid	mp, °C	$[\alpha]_D$, deg	Structure	Reference
		Nuphar alkaloids		
1. Thiobinupharidine $C_{30}H_{42}O_2N_2S$	129—130 Diperchl. 283–284	+49,4		1—5, 15
2. Neothiobinupharidine $C_{30}H_{42}O_2N_2S$	159–160 Diperchl. 320	−93,09		1–6, 12
3. Pseudothiobinupharidine $C_{30}H_{40}O_2N_2S$	Diperchl. 173—175	+186,2		2,3
4. Thiobideoxynupharidine $C_{30}H_{40}ON_2S$	Diperchl. 224–225	Perchl. +26,6		2,3
5. Allothiobinupharidine $C_{30}H_{42}O_2N_2S$	Diperchl. 320—325			2,3
6. Thionupharoline $C_{30}H_{42}O_3N_2S$	(Oil) Perchl. 170—173			7
7. 6,6'-Dihydroxythionuphlutine-A (nuphleine) $C_{30}H_{42}N_2O_4S$	Vitreous mass Diperchl. 225—226	+44,5		8, 9 10, 11
8. 6,6'-Dihydroxythionuphlutine-B $C_{30}H_{42}N_2O_4S$	Vitreous mass	—69		8

TABLE 1. (Continued)

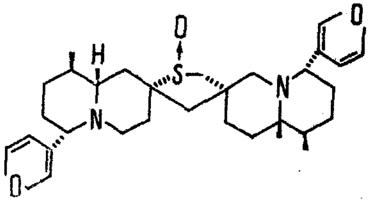
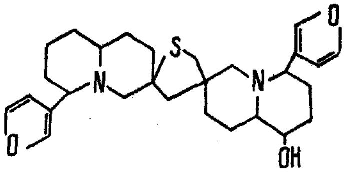
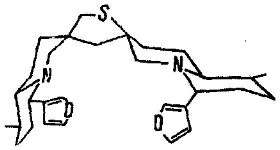
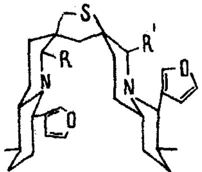
Name and composition of the alkaloid	mp, °C	$[\alpha]_D$, deg	Structure	Reference
9. Neothiobinupharidine sulfoxide $C_{30}H_{42}N_2O_3S$	240–242			12
10. 6-Hydroxythiobinupharidine	Perchl. 238–242 Diperchl. 265			15
11. Thionuphlutine-B				8,15
12. Thionupharodioline (Ia)	156–158		 I	16
13. Ethoxythiobinupharidine (Ib)	Perchl. 270			16
14. Diethoxythiobinupharidine (Ic)	Perchl. 230		a: R=R′=OH b: R=OEt; R′=H c: R=R′=OEt	16

TABLE 1. (Continued)

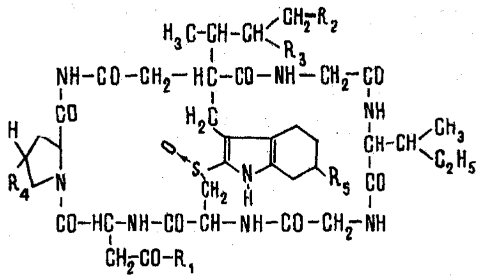
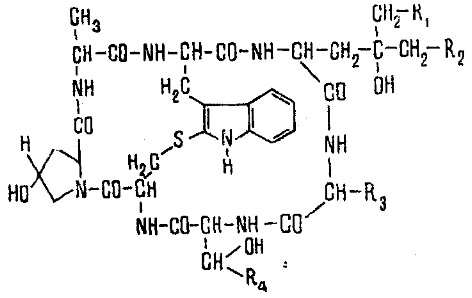
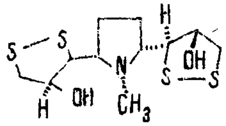
Name and composition of the alkaloid	mp, °C	$[\alpha]_D$, deg	Structure	Reference
	Peptide alkaloids			
15. α-Amanitine (Ia)			 I	19
16. β-Amanitine (Ib) 17. γ-Amanitine (Ic) 18. ε-Amanitine (Id) 19. ω-Amanitine (Ie) 20. Amanullinic acid (If) 21. Amanulline (Ig) 22. Amanine (Ih)			a : $R_1=NH_2$; $R_2=R_3=R_4=R_5=OH$ b : $R_1=R_2=R_3=R_4=R_5=OH$ c : $R_1=NH_2$; $R_2=H$; $R_3=R_4=R_5=OH$ d : $R_2=H$; $R_1=R_3=R_4=R_5=OH$ e : $R_1=NH_2$; $R_5=OH$; $R_2=R_3=R_4=H$ f : $R_1=R_4=R_5=OH$; $R_2=R_3=H$ g : $R_1=NH_2$; $R_4=R_5=OH$; $R_2=R_3=H$ h : $R_1=R_2=R_3=R_4=OH$; $R_5=H$	19 19 20 21 21 21 19,22
23. Phalloidine (IIa)			 II	17,23
24. Phalloine (IIb) 25. Phallisine (IIc) 26. Phallacidine (IId) 27. Phallisacine (IIe) 28. Phallacine (IIf)			a: $R_1=OH$; $R_2=H$; $R_3=R_4=CH_3$ b: $R_1=R_2=H$; $R_3=R_4=CH_3$ c: $R_1=R_2=OH$; $R_3=R_4=CH_3$ d: $R_1=H$; $R_2=OH$; $R_3=CH(CH_3)_2$; $R_4=COOH$ e: $R_1=R_2=OH$; $R_3=CH(CH_3)_2$; $R_4=COOH$ f: $R_1=R_2=H$; $R_3=CH(CH_3)_2$; $R_4=CCOH$	24 22 25 25 25
	Dithiolane derivatives			
29. Gerrardine $C_{11}H_{19}NO_2S_4$	180			26 27

TABLE 1. (Continued)

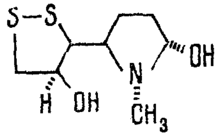
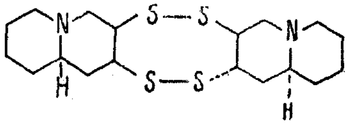
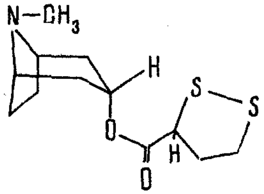
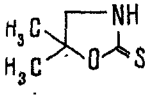
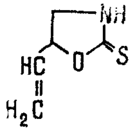
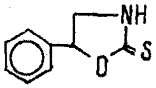
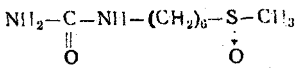
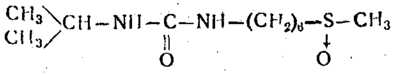
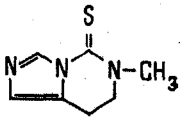
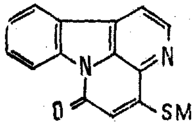
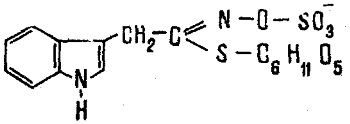
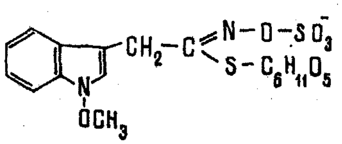
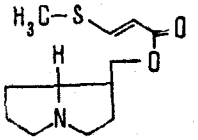
Name and composition of the alkaloid	mp, °C	$[\alpha]_D$, deg	Structure	Reference
30. Gerrardamine $C_8H_{15}NOS_2$	Amorph.			26
31. Gerrardoline $C_8H_{15}NO_2S_2$	60			26
32. Cassipourine $C_{14}H_{22}N_2S_4$	212			28
33. Brugine $C_{12}H_{19}NO_2S_2$	Vitreous mass			29
Oxazolidinethione derivatives:				
34. 5,5-Dimethyloxazolidine-2-thione C_5H_9NOS	108,5–109,5			30
35. Goitrin (*l*-5-vinyloxazolidine-2-thione) C_5H_7ONS	50	−70,5		31 34
36. Resedinine C_9H_9NOS	119–121			33

TABLE 1. (Continued)

Name and composition of the alkaloid	mp, °C	$[\alpha]_D$, deg	Structure	Reference
		Thiourea and urea derivatives		
37. Diptocarpaine $C_8H_{18}N_2O_2S$	121–125	−80,33	 $NH_2-\underset{\overset{\parallel}{O}}{C}-NH-(CH_2)_6-\underset{\overset{\downarrow}{O}}{S}-CH_3$	35
38. Diptocarpamine $C_{11}H_{24}N_2O_2S$	100–101	−58,21	 $\begin{matrix}CH_3\\CH_3\end{matrix}\!>CH-NH-\underset{\overset{\parallel}{O}}{C}-NH-(CH_2)_6-\underset{\overset{\downarrow}{O}}{S}-CH_3$	36 35 37
39. Diptocarpidine $C_{15}H_{32}O_3N_2S_2$	135–136	−70,54		35
40. Base No. 5	bp 193–195	−49,23		35
41. Diptocarpine sulfate	300			35
42. Diptocarpinine	91–92			36
43. Zapotidine $C_7H_9N_3S$	96–98			38
		Miscellaneous alkaloids		
44. 4-Methylthiocanthin-6-one				39
45. Glucobrassicine	140–142	−13,3		40
46. Neoglucobrassicine	Brucine salt 175			40
47. Planchonelline	(Oil)	+9		41
		Uncharacterized alkaloids		
48. $C_{12}H_{14}N_2O_4S$	198–202	−19		42
49. $C_{30}H_{42}N_2O_3S$	238			42

with thiobinupharidine [9]. Sulfur-containing alkaloids have been isolated by T. N. Il'inskaya and A. D. Kuzovkov from N. luteum [10]. In addition to the known thiobinupharidine and neothiobinupharidine, these workers isolated an alkaloid containing α-carbinolamine groups to which they gave the new name of nuphleine. On reduction with sodium tetrahydroborate, the latter was converted quantitatively into thiobinuphlaridine. On detailed spectroscopic study, nuphleine proved to be identical with 6,6'-dihydroxythionuphlutine A [11].

This group of alkaloids also includes neothiobinupharidine S-oxide [12], the structure of which was established on the basis of the results of a comparative study of the spectra of the base and of neothiobinupharidine and deoxynupharidine, and also as the result of passage to neothiobinupharidine (PCl_3 in ethyl acetate) and back by oxidation (H_2O_2 in acetic acid).

As can be seen from what has been stated above, all the sulfur-containing alkaloids of Nuphar are closely related to one another, include a tetrahydrothiophene ring, and are derivatives of thiobinupharidine, thionuphlutine B, and neothiobinupharidine, which are stereoisomers of one another. Consequently, the structure and stereochemistry of these three alkaloids have been considered in many publications. The definitive establishment of the structure of thiobinupharidine, performed in parallel with a study of the structure of neothiobinupharidine, had great value. According to their IR spectra, they contain a trans-quinolizidine system, a monosubstituted furan system, a CH_3 group, and a $-H_2C-S-C-$system not attached to the furan ring. Peaks in the NMR spectra show the presence of furan and CH_3 groups.

A great role in the proof of the structures of these alkaloids was played by the study of their mass spectra [13]. The mixture of bases obtained in the desulfuration of neothiobinupharidine and thiobinupharidine under very severe conditions was investigated by mass spectrometry. The spectrum of each sample obtained on fractional evaporation within the ion source was identical with that of deoxynupharidine. On this basis it was concluded that each of the two alkaloids consists of two deoxynupharidine skeletons connected by one $-C-C-$ and one $-C-S-C-$bridges. On a careful study of the structures of fragments with m/e 359, 230, 178, 186, and 94, the partially correct structure of the alkaloids was established, but only in 1965 did Birnbaum show, on the basis of the results of an x-ray structural analysis, the structure of neothiobinupharidine [14] (see Table 1), from which it followed that both quinolizidine systems in the alkaloid molecule are trans-linked, all the six-membered rings are present in the chair conformation, and 20 of the atoms forming rings are located almost in one plane. Perpendicular to this plane are the tetrahydrothiophene ring and two furan rings, one of which is parallel to the tetrahydrothiophene ring and the other perpendicular to it. Both furan rings and both $-CH_3$ groups are equatorial and C-18 is equatorial with respect to both quinolizidine systems, while C-17 and S are axial.

For thiobinupharidine, on the basis of the structure of neothiobinupharidine, a structure has been proposed in which the two quinolizidine systems are symmetrical. In 1973, a special study was made of the structure of thiobinupharidine with the aid of x-ray structural analysis [15], and structure 1 (see Table 1) was established for it.

From an ethanolic extract of the fungus Amanita phalloides (death cap) German scientists have isolated a whole series of toxic principles [17] which, from the chemical point of view and in relation to toxicity, can be divided into two groups: the aminitine group – toxins which give a bright violet coloration with cinnamaldehyde – and the less poisonous phalloidine group, the toxins of which give a very weak blue coloration. The representatives of the two groups also differ in their UV spectra [18] (Fig. 1).

Chemically, the substances isolated are cyclopeptide bases including an indole nucleus. The majority of them contain a sulfur atom as a component of the amino acid cysteine, while the toxins of the aminitine group have the nature of sulfoxides. The structures of these substances were shown by hydrogenolytic desulfuration over Raney nickel, and also by acid hydrolysis followed by the deciphering, the identification, and the determination of the sequence of the amino acids liberated on hydrolysis (see Table 1).

Dithiolane Derivatives. This group of sulfur-containing alkaloids is characteristic for the plants of some species of the family Rhizophoraceae. Thus, from two species of Cassipourea have been isolated four sulfur-containing bases [26]: gerrardine, gerrardamine, and gerrardoline were found in C. gerrardii and cassipourine in C. gummiflua.

To prove the structure of this group of alkaloids we used desulfuration over Raney nickel followed by a study of the dethio products. From the products of the desulfuration of gerrardine with Raney nickel we isolated dimethylaminodecane-2,9-diol and a substance that proved to be decane-2,9-diol, which showed the presence of a continuous chain of 10 carbon atoms, and demonstrated the position of the $-OH$ group and the site of attachment of the dithiolane ring.

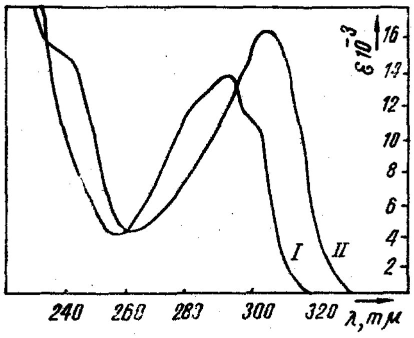
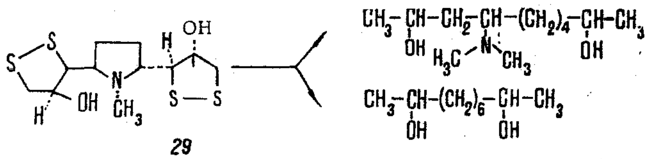


Fig. 1. UV spectra of phalloidine, phalloine, and phallacidine (I) and of α- and β-amantines (II) in water.

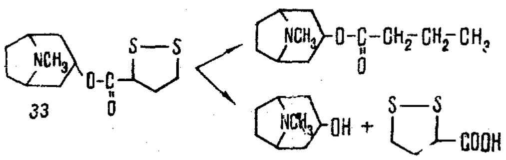
The structure of gerrardine was established by a study of the mass spectrum of the base itself and of the products of its desulfuration. The results of x-ray structural investigation confirmed structure 29 which had been proposed for gerrardine and showed the trans arrangement of the dithiolane rings and of the OH groups [27]:



29

The catalytic desulfuration over Raney nickel or another alkaloid – cassipourine [28] – yielded pyrrolizidine. The four sulfur atoms present in the molecule form a tetrathiooctane ring. The structure of cassipourine was shown by the performance of a whole series of chemical reactions. Thus, on distillation with zinc dust hydrogen sulfide and pyrrolo[1,2-a]pyrrolidine was obtained, oxidation with concentrated nitric acid gave pyrrolizidinedisulfonic acid N-oxide, and from the products of Hofmann degradation was isolated a substance identified as 2-allyl-1-methylpyrrole. On the basis of the reactions performed, a study of spectral characteristics, and the results of x-ray structural analysis, structure 32 (see Table 1) was established for cassipourine.

Another sulfur-containing alkaloid of the family Rhizophoraceae, isolated from Brunguiera sexangula is brugine [29]. Desulfuration of the alkaloid over Raney nickel led to tropine n-butyrate. Alkaline hydrolysis yielded the amino alcohol tropine and 1,2-dithiolane-3-carboxylic acid:

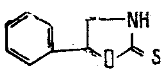


33

On the basis of the reactions performed and spectral characteristics, structure 33 is proposed for brugine.

Oxazolidinethione Derivatives. Few alkaloids of this group have been isolated from plants. At the present time, only three such alkaloids are known: 5,5-dimethyloxazolidine-2-thione [30], goitrin (*l*-5-vinyloxazolidine-2-thione) [31], and resedinine (5-phenyloxazolidine-2-thione) [32]. The heterocyclic skeleton of these bases consists of an oxazolidine thione nulceus substituted in position 5. The fact that these alkaloids belong to this group has been clearly demonstrated by spectroscopy. Thus, their UV spectra show absorption maxima at 240 nm, and in an alkaline medium a slight hypsochromic shift is observed. The IR spectra, which are characterized by groups of bands at 3425, 3155, 1538, 1508, and 1167 cm^{-1}, show the function of the heteroatoms.

The alkaloid resedinine is a thio analog of resedine [33]. On reduction with lithium tetrahydroaluminate, the oxazolidinethione ring opens with the simultaneous reduction of the position of cleavage of the bonds. From resedinine (36) was obtained β-hydroxy-β-phenylethyl(methyl)amine, which definitely showed the structure of the alkaloid.



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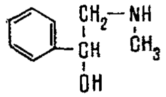
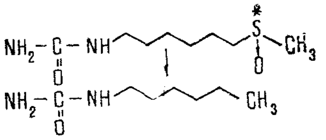


The alkaloid goitrin has been isolated from the edible root of the turnip and also from the seeds of many other species of plants of the genus Brassica (family Cruciferae) [34]. It has been shown spectrophotometrically that goitrin is present in all the species of the family Cruciferae studied with the exception of mustard seeds and cauliflower.

Alkaloids with a sulfur atom in the side chain are more numerous and include various classes of compounds. Such are derivatives of thiourea, urea, pyrrolizidine, and indole.

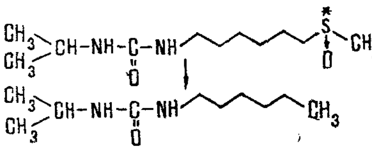
As already mentioned, plants of the family Cruciferae produce sulfur-containing compounds. A clear example of this is Dipthychocarpus strictus, belonging to this family. Separation of the combined bases of the epigeal part yielded seven compounds [35].

The two alkaloids diptocarpaine and diptocarpamine, which are similar in their chemical properties, proved to be N-alkylurea derivatives. In both these bases, the sulfur was present in the sulfoxide form, as was shown by spectral characteristics and the results of a number of chemical reactions. The existance of optical activity in these alkaloids and the absence of it in their reduction products is also explained by the presence in them of sulfoxide groups in which the sulfur atom, bound to two nonequivalent radicals and one electron pair, playing the role of fourth substituent, is asymmetrical [36]. In both alkaloids hydrogenolytic desulfuration over Raney nickel has been used. In this way, diptocarpaine yielded an optically inactive substance of neutral character which proved to be N-n-hexylurea.

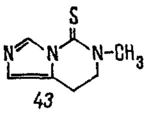


In this reaction, diptocarpamine gave N-n-hexyl-N-isopropylurea.

The chemical reactions performed and the analysis of the spectral characteristics both of the alkaloids themselves and of their dethio products made it possible to establish the following structures for the two bases [36, 37]:



A rare thiourea derivative is the alkaloid zapotidine from seeds of the tree Cassimiroa edulus (family Rutaceae), the type of ring system in the molecule of which has not hitherto been found in other natural compounds. On being boiled in silver nitrate solution in the presence of alkali, the alkaloid gives a urea derivative $C_7H_9N_3O$. On reduction with lithium tetrahydroaluminate, N,N'-dimethylhistamine was obtained, and boiling in concentrated caustic soda solution yielded N-methylhistamine. On the basis of the NMR spectrum and chemical reactions, structure 43 is proposed for the alkaloid [38]:



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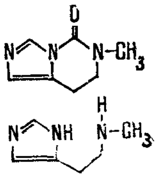

From the plant Pentaceras australis (family Rutaceae), Australian scientists have isolated methylthiocanthinone [39], in which the sulfur is present in a methylthio group. On alkaline hydrolysis, the alkaloid is converted into the known 4-hydroxycanthin-6-one.

Two glycoalkaloids that are derivatives of tryptophan have been isolated from Brassica seeds – glucobrassicine and neoglucobrassicine, which, on enzymatic cleavage, give thiocyanate, glucose, indolylacetonitrile, and indolyacetic acid [40].

The presence of glucobrassicine and of neoglucobrassicine is characteristic for many species of the families Cruciferae, Capparidaceae, Tovaricaceae, and Resedaceae. Thus, the study of the seeds of 14 species of these families has shown that they all contain glucobrassicine or neoglucobrassicine or their esters [40].

Among the bases of the pyrrolizidine group has been found a single sulfur-containing alkaloid – planchonelline – which is the trans-β-methylthioacrylic ester of laburnine [41]. Hydrolysis of the alkaloid gave laburnine and a thio acid which proved to be trans-β-methylthioacrylic acid.

Thus, sulfur-containing alkaloids, in spite of their small number, are found among many classes of natural organic compounds. The proof of their structure reduces to obtaining desulfuration products followed by the characterization of these products. Here, a large amount of information is given by a careful study of the mass spectrum.

The presence of sulfur in an alkaloid is easily determined without the use of analytical methods. By mass spectrometry, from the presence in the spectrum of the peaks of an isotopic sulfur ion it is possible not only to determine whether the substance contains sulfur or not but also to carry out the analysis quantitatively, with the possibility of distinguishing sulfur-containing and sulfur-free fragments, which considerably facilitates the determination of the structures of unknown compounds. On the other hand, the mass-spectrometric fragmentation of sulfur-containing alkaloids is considerably complicated by the presence of numerous rearrangement ions in the spectrum.

Because of the diversity of their chemical structures, the spectrum of the pharmacological action of sulfur-containing alkaloids is very wide.

Concerning the pharmacology of the Nuphar alkaloids, it can be stated that the first reports of the use of extracts from the rhizomes of the plant in inflammation of the small intestine, gingivitises, and skin diseases was published as early as 1945 [43]. Later, it was established that a representative of this group of alkaloids nuphleine (6,6'-dihydroxythiobinupharidine) possesses protistostatic and spermicidal activity, inhibiting the growth of Trichomonas vaginalis, and it also suppresses the growth of fungi and Gram-positive bacteria [44]. A high activity of 6,6'-dihydroxythiobinupharidine against eight species of pathogenic fungi has been reported [43].

It is interesting that in the monomers the high biological activity characteristic of the dimeric sulfur-containing alkaloids of Nuphar completely disappears and is not manifested. This can apparently be explained by the presence of the tetrahydrothiophene ring in the dimers. According to Prof. Watson, sulfur-containing alkaloids that are derivatives of dithiolane – gerrardine and cassipourine – possess pronounced activity against certain species of Salmonella, which belong to the family Enterobacteriaceae. The effect proved to be bactericidal but not inhibitory [26]. The biological effect is apparently shown when two dithiolane rings are present, isolated, as in gerrardine, and forming a peculiar ring structure including four sulfur atoms, as in cassipourine. Neither gerrardoline nor gerrardamine – monomeric forms corresponding to gerrardine – possessed antibacterial properties.

It has been reported that the seeds of the plant from which the alkaloids zapotidin was isolated possess sedative, hypotensive, and also hypnotic properties.

An antithyroid activity of alkaloids of the oxazolidinethione group has been found. It has been reported that cabbages, turnips, grape seeds, soybeans, and groundnuts causes an increase in the activity of the thyroid gland [34], but attempts to isolate the active principal from them were unsuccessful.

Antithyroid compounds isolated from plants are also known, such as thiourea from Laburnum anagyroides and 5,5-dimethyloxazolidine-2-thione from the seeds of Conringia orientalis [30].

It is known that some foods delay the absorption of radioactive iodine in the same way as antithyroid substances. The most effective in this respect have proved to be the rutabaga or swede [34], and also fresh cabbage leaves [30], from which goitrin has been isolated. A comparative study of the thyroid activity of oxazolidine-2-thione, 5,5-dimethyloxazolidine-2-thione, and *l*-5-vinyloxazolidine-2-thione (goitrin) has shown that the latter possesses five times greater activity, from which it follows that the presence of a vinyl group in the C-5 position of goitrin considerably increases its activity.

On considering the pharmacological properties, the conclusion involuntarily suggests itself that sulfur-containing alkaloids are characterized to some degree or other, or should be characterized (if this has not yet been investigated), by microbiological activity.

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