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BISBENZYLISOQUINOLINE ALKALOIDS

O. N. Tolkachev, E. P. Nakova, and R. P. Evstigneeva

UDC 547.944/945

Distribution in Nature

Bisbenzylisoquinoline alkaloids form a large group of natural bases found in plants of the families of Menispermaceae, Berberidaceae, Ranunculaceae, Lauraceae, Annonaceae, Hernandiaceae, Magnoliaceae, and Nymphaeaceae.

At the present time, more than 150 bisbenzylisoquinoline bases are known the structure of which includes two benzylisoquinoline fragments connected by one, two, or three ether bonds. The number of ether bonds and the positions which they link are used as criteria for classifying these alkaloids. As exceptions, compounds are found with a carbon–carbon bond between the benzyl residues for example, rodiasine, ocotine, and tiliacorine

In recent years, with the development of instrumental methods of determining structure, and also in connection with the discovery of a series of active drugs among bisbenzylisoquinoline alkaloids interest in this class of natural compounds has risen considerably. The list of bimolecular ether alkaloids (see Table 1) is not limited only to bisbenzylisoquinoline bases. It is constantly being supplemented by new types of bases genetically connected with them: benzylisoquinoline-aporphine (see the reviews [120-122]), benzylisoquinoline-proaporphine, bishomobenzylisoquinoline, benzylisoquinoline-benzazpine, aporphine-pavine and others (I-VIII). This shows that the chemistry of these alkaloids is far from being exhausted.

Chemical Methods of Studying the Structure of the Bisbenzylisoquinoline Alkaloids

The chemical methods of determining the structure of bisbenzylisoquinoline alkaloids consist in the cleavage of their molecules to give simpler fragments of known structure, which provides a possibility of determining the positions of the substituents and of the ether bridges. For this purpose oxidation, reduction, Hofmann degradation, etc., are used. As a rule, phenol-containing alkaloids are previously protected by O-methylation or O-ethylation, and are then cleaved into simpler fragments. Quaternary ammonium salts can, where necessary, be converted into tertiary bases with a yield of 64-84% by heating them with ethanolamine [127] or with sodium thiophenolate [105].

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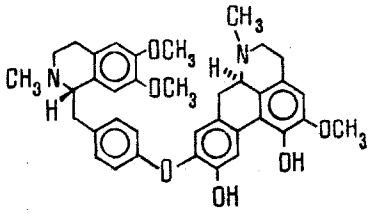
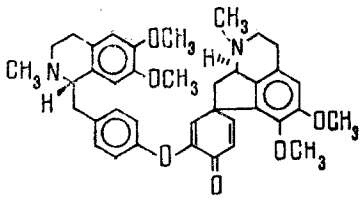
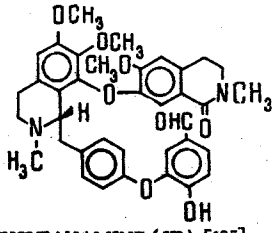


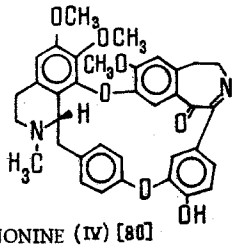
PAKISTANINE (I) [123]



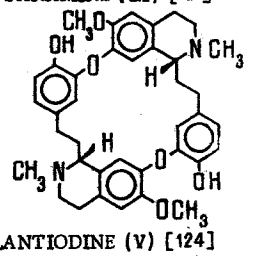
PAKISTANAMINE (II) [123]



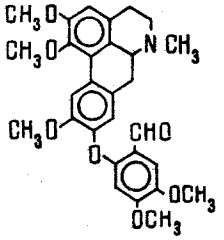
BALUCHISTANAMINE (III) [125]



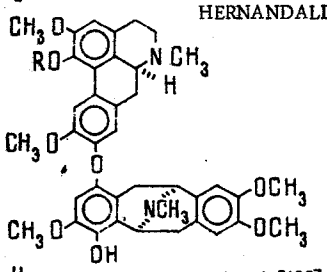
STEPINONINE (IV) [80]



(−)-MELANTIODINE (V) [124]



HERNANDALINE (VI) [126]



R=H PENNSYLPAVINE (VII) [126]

R=CH$_3$ PENNSYLPAVOLINE (VIII)

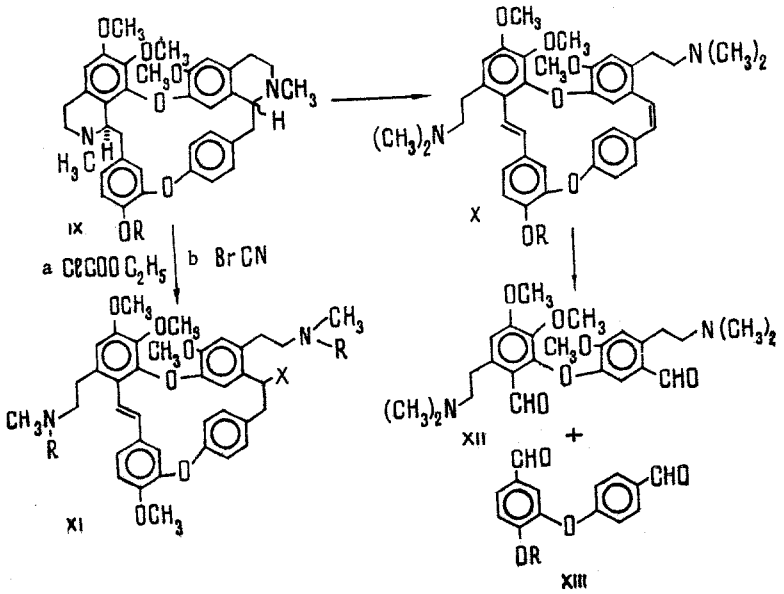
In the Hofmann degradation of quaternary ammonium derivatives of alkaloids in the first stage of cleavage, unsaturated bases (methines) are formed. For the bisbenzylisoquinoline bases it has been shown that both the ease and the direction of Hofmann cleavage depends on the structure and stereoconfiguration of the alkaloid molecule. Bases of the oxyacanthine series give a 70-90% yield of optically inactive bisstilbene derivatives in which one double bond has the cis configuration and the other the trans configuration. Conversely, bases of the berbamine (R, S) series (IX) are converted under the conditions of this reaction into bisstilbene derivatives (X) with a yield of only 6-10% [43].

The cleavage of alkaloids on their reaction with chloroformic ester at room temperature takes place similarly. However, in this case, berbamine methyl ether forms a chlorine-containing monostilbene diurethane (XI, R = $COOC_2H_5$, X = Cl) in which the double bond has the trans orientation. An isoquinoline ring unsubstituted in position 8 is open to the formation of a chlorine-containing urethane and with occurrence of a Walden inversion at $C_{1'}$.

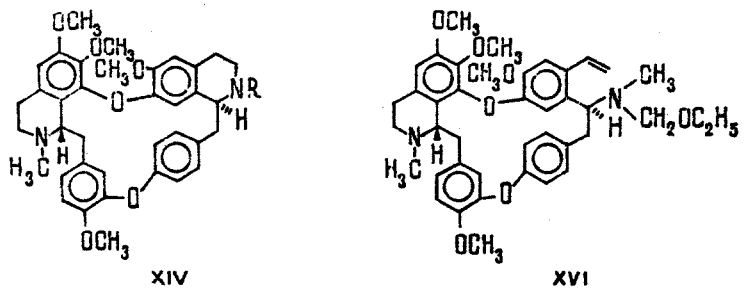
Under the action of hot ethanolic caustic potash, no second double bond is formed, and the halogen is simply replaced by a hydroxy group. The authors concerned explain the impossibility of the formation of a second double bond under these conditions by the assumption that the reaction centers in the transition state cannot adopt an anticoplanar conformation [129]. The Braun cleavage of isotetrandrine (R, S) with cyanogen bromide takes place similarly with the formation of the bromine-containing stilbene (XI, R = CN, X = Br) [130].

The hydroxyurethane (XI, R = $COOC_2H_5$, X = OH) is reduced by lithium tetrahydroaluminate to the hydroxystilbene (XI, R = CH_3, X = OH) which is similar to the methylmethine obtained when the alkaloid is subjected to Hofmann degradation.

Ozonolysis of the bisstilbene methine base (X) leads to the formation of the simpler aldehyde-group-containing fragment (XII) and (XIII).



The reaction of tetrandrine (XIV, R = CH_3) with methyl chloroformate takes place by a different route. Monodemethylation takes place without the opening of the isoquinoline ring, and a monourethane (XIV, R = $COOCH_3$) is formed, and this, on alkaline saponification, is converted into cycleanorine (XIV, R = H), isolated from Cyclea peltata [28].



It must be mentioned that, on extraction from plant raw material with methylene chloride, alkaloids of this type are capable of reacting with the solvent to form chloromethylammonium chlorides. Under these conditions, tetrandrine forms a N'-monoquaternary salt (XV), which with potassium tert-butanolate and propanethiol in dimethylacetamide at room temperature forms cycleanorine in good yield. Conversely, when the quaternary salt is heated with an ethanolic solution of sodium ethanolate, the reaction takes place by the classical route with the cleavage of the ring and the formation of a methine base of structure (XVI) [28].

The methylation with diazomethane in methanol of the phenolic mono- and bisquaternary salts of tubocurarine (XVII, R' = H, R" = CH_3), (+)-isotubocurarine (XVII, R' = CH_3, R" = H), and chondrocurarine (XVII, R' = R" = CH_3) is also accompanied by the cleavage of the isoquinoline nucleus containing the quaternary nitrogen atom with the formation of the methine bases (XVIII-XX). Here, as can be seen from the Scheme, the direction of the reaction depends on the substitution in the isoquinoline nuclei and the stereoconfiguration [131].

TABLE 1. Main Representatives of the Bisbenzylisoquinoline Alkaloids Found in Natural sources

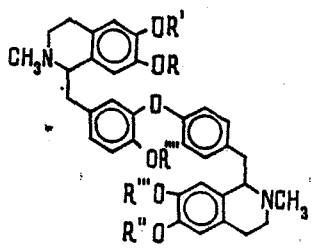
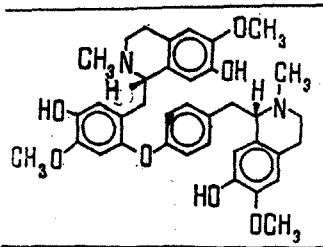
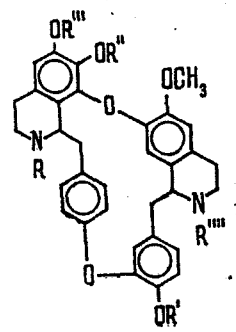
Formula	No.	R	R′	R″	R‴	R⁗	Name	Composition	mp, °C	$[\alpha]_D$, deg	Configuration C-1	Configuration C-1′	Source of isolation and structure
	1	H	CH_3	CH_3	H	H	N,N′-demethyl Lindoldhamine	$C_{37}H_{38}N_2O_6$	183—186	−35 (EtOH)	R	R	Lindera oldhamii [1]
	2	H	CH_3	CH_3	H	H	Magnoline	$C_{36}H_{40}N_2O_6$	178—179	−9,6 (Py)	S	R	Michelia (Magnolia) fuscata [2]
	3	H	CH_3	CH_3	H	H	Berbamunine	$C_{36}H_{40}N_2O_6$	190—191	+25,6 (Py)	R	S	Berberis amurensis [3]
	4	CH_3	H	H	CH_3	H	Dauricoline	$C_{36}H_{40}N_2O_6$			R	R	Menispermum dauricum [4]
	5	H	CH_3	H	H	CH_3	Espinine	$C_{36}H_{40}N_2O_6$	123—125	+25 (chl.)	R	S	B. laurina [5]
	6	H	CH_3	H	CH_3	CH_3	Espinidine	$C_{37}H_{42}N_2O_6$	Amorph.	+31 (chl.)	R	S	B. laurina [5]
	7	CH_3	CH_3	CH_3	CH_3	H	N-Demethyldauricine N-nor	$C_{37}H_{42}N_2O_6$		−98 (MeOH)	R	R	M. canadense [6]
	8	H	CH_3	CH_3	H	CH_3	Cuspidaline	$C_{37}H_{42}N_2O_6$	Oil	−48 (chl.)	R	R	Limacia Cuspidata [7—8]
	9	CH_3	CH_3	H	CH_3	H	Daurinoline	$C_{37}H_{42}N_2O_6$	100—103	−108(MeOH)	R	R	M. dauricum [4], M. canadense [6]
	10	CH_3	CH_3	CH_3	H	CH_3	Northalibrine	$C_{37}H_{42}N_2O_6$	—	+47 (chl.)	S	S	Thalictrum rochebrunianum [9]
	11	CH_3	H	CH_3	CH_3	H	Dauricinoline	$C_{37}H_{42}N_2O_6$			R	R	M. dauricum [11]
	12	CH_3	CH_3	CH_3	CH_3	H	Dauricine	$C_{38}H_{44}N_2O_6$	100—103	−139(MeOH)	R	R	M. dauricum [4, 6]
	13	CH_3	CH_3	CH_3	H	CH_3	Thalibrine	$C_{38}H_{44}N_2O_6$	—	+47 (chl.)	S	S	Th. rochebrunianum [9]
	14	CH_3	CH_3	CH_3	CH_3	CH_3	O-Methyldauricine	$C_{39}H_{46}N_2O_6$	76—78 (decomp.)	−79 (EtOH)	R	R	M. dauricum [4, 10]
	15						Magnolamine	$C_{37}H_{42}N_2O_6$	117—119	+180(EtOH)	S	S	Michelia (Magnolia) fuscata [12—13]
	16	H	H	H	CH_3	H	N,N′-Bisnoraromoline	$C_{34}H_{34}N_2O_6$	206 (vac.)	+177 (HCl)	S	R	Pycnarrhena ozantha [14]
	17	CH_3	H	H	CH_3	H	Trilobamine (daphnoline)	$C_{35}H_{36}N_2O_6$	195—196	+459 (chl.)	S	R	Daphnandra micranta [15], Abuta splendida [16]
	18	CH_3	H	H	CH_3	CH_3	Aromoline	$C_{36}H_{38}N_2O_6$	182—183 (224)	+327 (chl.)	S	R	D. micranta [15]
	19	CH_3	CH_3	H	CH_3	H	Daphnandrine	$C_{36}H_{38}N_2O_6$	280	+475 (chl.)	S	R	D. micranta [15]
	20	CH_3	H	CH_3	CH_3	H	Sepeerine (octoteamine)	$C_{36}H_{38}N_2O_6$	221—222	+392 (chl.)	S	R	Ocotea rodiaei [17—19]
	21	CH_3	H	CH_3	CH_3	H	Demerarine	$C_{36}H_{38}N_2O_6$	222—223	−162 (chl.—MeOH)	S	S	O. rodiaei [17—18]
	22	CH_3	CH_3	CH_3	H	H	Thalmine	$C_{36}H_{36}N_2O_6$	251—252	−219 (chl.)	S	S	Th. minus [20]
	23		H	CH_3	CH_3	CH_3 $\Delta^{1,2}$	Hypoepistephanine	$C_{36}H_{36}N_2O_6$	256—257	+184 (chl.)	—	R	Stephania japonica [21]
	24		CH_3	CH_3	CH_3	$\Delta^{1,2,1',2'}$	Stebisimine	$C_{36}H_{36}N_2O_6$	233—235	0	—	—	S. japonica [22]
	25	CH_3	H	—CH_2—		CH_3	Cepharanoline	$C_{36}H_{36}N_2O_6$	270 (decomp.)	+319(chl.)	S	R	S. cepharantha [23]
	26	CH_3	H	CH_3	CH_3	CH_3	Oxycanthine	$C_{37}H_{40}N_2O_6$	216—217	+279 (chl.)	S	R	B. integerrima [24]
	27	CH_3	H	CH_3	CH_3	CH_3	Repandrine	$C_{37}H_{40}N_2O_6$	255 (decomp.)	−106 (chl.)	S	S	D. repandula [25]
	28	CH_3	CH_3	H	CH_3	CH_3	(+)-Thalrugosamine	$C_{37}H_{40}N_2O_6$	122—125	+280 (MeOH)	R	S	Th. rugosum [26]
	29	CH_3	CH_3	H	CH_3	CH_3	Limacusine	$C_{37}H_{40}N_2O_6$	236—237	+110 (chl.)	R	R	L. cuspidata [27]

TABLE 1 (continued)

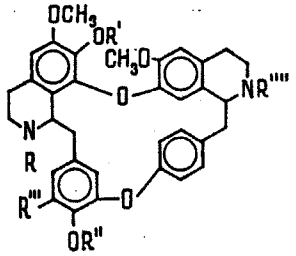
Formula	No.	R	R′	R″	R‴	R⁗	Name	Composition	mp, °C	$[\alpha]_D$, deg	Configuration C-1	Configuration C-1′	Source of isolation and structure
	30	CH_3	CH_3	H	CH_3	CH_3	Homoaromoline	$C_{37}H_{40}N_2O_6$	236–237	+371 (chl.)	S	R	A. splendida [16]
	31	CH_3	CH_3	H	CH_3	CH_3	Cycleapeltine (faralaotrine?)	$C_{37}H_{40}N_2O_6$	232—234	—106 (chl.)	S	S	Cyclea peltata [28] Colubria faralaotra [34]
	32	CH_3	CH_3	—CH_2—		CH_3	Cepharathine	$C_{37}H_{38}N_2O_6$	145—155	+277 (chl.)	S	R	S. cepharantha [29]
	33	CH_3	CH_3	CH_3	CH_3	$\Delta^{1',2'}$	Coclobine	$C_{37}H_{38}N_2O_6$	Аморф.	+123 (chl.)	S	—	Cocculus trilobis [30]
	34		CH_3	CH_3	CH_3	$CH_3\Delta^{1,2}$	Epistephanine	$C_{37}H_{38}N_2O_6$	Amorph. 202–204	+226 (chl.)	—	R	S. japonica [31]
	35	CH_3	CH_3	CH_3	CH_3	CH_3	Obaberine	$C_{38}H_{42}N_2O_6$	139—140	+302 (chl.)	S	R	B. tschonokiana [32]
	36	CH_3	CH_3	CH_3	CH_3	CH_3, octadehydro	Pheantharine	$C_{38}H_{36}N_2O_6 \cdot Cl_2$	215—220	0	—	—	Pheanthus obracteodatus [33]
	37	H	H	H	H	CH_3	2-N-Norobamegine	$C_{35}H_{36}N_2O_6$	188—190 (decomp.)	+146 (HCl)	R	S	Pycnarrhena ozantha [14, 35]
	38	H	CH_3	H	H	CH_3	2-N-Norberbamine	$C_{35}H_{38}N_2O_6$	166—168	+117 (chl.)	R	S	P. australiana [35]
	39	CH_3	H	H	H	CH_3	Obamegine (stepholine)	$C_{36}H_{38}N_2O_6$	172 (decomp.)	+241 (chl.)	R	S	Th. rugosum [36]
	40	CH_3	H	H	H	CH_3	Krukovine	$C_{36}H_{38}N_2O_6$	182—183	—180 (chl.)	R	R	A. splendida [16]
	41	CH_3	H	H	H	CH_3	Atherospermoline	$C_{36}H_{38}N_2O_6$	183—188	+202 (chl.)	S	S	Atherosperma moschatum [37—38]
	42	CH_3	H	CH_3	H	CH_3	Thalrugosine	$C_{37}H_{40}N_2O_6$	212–214(dec.)	+128(MeOH)	R	S	Th. rugosum [39]
	43	CH_3	CH_3	H	H	CH_3	Berbamine	$C_{37}H_{40}N_2O_6$	156(EtOH) 197—200	+109 (chl.)	R	S	Krung Kha Mao [40], S. cepharantha [29]
	44	CH_3	CH_3	H	H	CH_3	Penduline	$C_{37}H_{40}N_2O_6$	192—194	+265 (chl.)	S	S	Cocculus pendulus [41]
	45	CH_3	CH_2	H	H	CH_3	Pycnamine	$C_{37}H_{40}N_2O_6$	183	—283 (chl.)	R	R	Pycnarrhena manilensis [42—43]
	46	CH_3	H	CH_3	H	CH_3	Fangchinoline	$C_{37}H_{40}N_2O_6$	171—173	+255 (chl.)	S	S	Cyclea peltata [44—46]
	47	CH_3	H	CH_3	H	CH_3	Limacine	$C_{37}H_{40}N_2O_6$	154—156	—212 (chl.)	R	R	Limacia cuspidata [27, 34]
	48	CH_3	CH_3	CH_3	H	H	Cycleanorine	$C_{37}H_{40}N_2O_6$	170—172	+308 (chl.)	S	S	Cyclea peltata [28]
	49	CH_3	H	CH_3	H	CH_3	Cycleadrine	$C_{37}H_{40}N_2O_6$	160—162	0	RS		C. peltata [28]
	50	H	CH_3	CH_3	H	CH_3	2-Nortetrandrine	$C_{37}H_{40}N_2O_6$	222—226	+335(chl.)	S	S	Ocotea rodiaei [19]
	51	CH_3	H	—CH_2O—		CH_3	Nortenuipine	$C_{37}H_{38}N_2O_6$	260	+236 (chl.)	S	S	D. tenuips [47]
	52	CH_3	H	—CH_2O—		CH_3	(—)-Demthyltenuipine	$C_{37}H_{38}N_2O_6$	211	—218 (chl.)	R	R	D. tenuips [48]
	53	CH_3	CH_3	—CH_2O—		CH_3	(+)-Tenuipine	$C_{38}H_{40}N_2O_6$	219	+224 (chl.)	S	S	D. tenuips [48]
	54	CH_3	CH_3	—CH_2O		CH_3	(—)-Tenuipine	$C_{38}H_{40}N_2O_7$	140—145	—258 (chl.)	R	R	D. tenuips [47]
	55	CH_3	CH_3	—CH_2O		CH_3	Repandinine (±)-tenuipine)	$C_{38}H_{40}N_2O_7$	243	0	RS		D. repandula [47, 48]
	56	CH_3	CH_3	—CH_2O		CH_3	(+)-Isotenuipine	$C_{38}H_{40}N_2O_7$	239–241	+129 (chl.)	R	S	D. tenuips [50]
	57	CH_3	CH_3	CH_3	H	CH_3	Pheanthine (*l*-tetrandrine)	$C_{38}H_{42}N_2O_6$	216—217	—284 (chl.)	R	R	Pheanthus [49, 51]
	58	CH_3	CH_3	CH_3	H	CH_3	d*l*-Tetrandrine	$C_{38}H_{42}N_2O_6$	250—252	0	RS		Krung Kha Mao [40] C. peltata [44]
	59	CH_3	CH_3	CH_3	H	CH_3	Isotetrandrine	$C_{38}H_{42}N_2O_6$	182—183	+144 (chl.)	R	S	S. cepharantha [29]
	60	CH_3	CH_3	CH_3	H	CH_3	d-Tetrandrine	$C_{38}H_{42}N_2O_6$	217—218	+285 (chl.)	S	S	C. peltata [28, 45], Krung Kha Mao [40]
	61	$(CH_3)_2Cl$	CH_3	CH_3	H	CH_3	Cycleahomine chloride	$C_{39}H_{45}N_2O_6Cl$	190—194	+103 (chl.)	S	S	C. peltata [28]

TABLE 1 (continued)

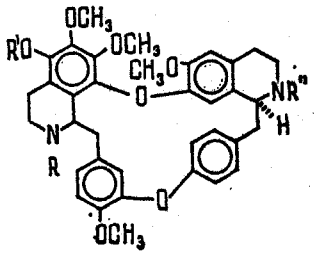
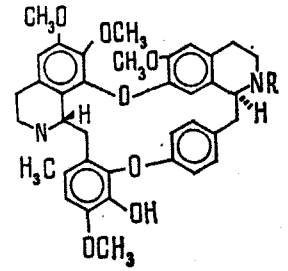
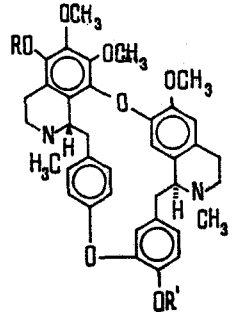
Formula	No.	R	R′	R″	R‴	R⁗	Name	Composition	mp, °C	$[\alpha]_D$, deg	Configuration C-1	Configuration C-1′	Source of isolation and structure
	62	CH_3	H			$\Delta^{1',2'}$	Thalsimidine	$C_{37}H_{38}N_2O_7$	195	+48 (chl.)	S	—	Thalictrum simplex [52—54]
	63	CH_3	CH_3			$\Delta^{1',2'}$	Thalsimine	$C_{38}H_{40}N_2O_7$	149—150	+27.5(EtOH)	S	—	Th. simplex [53—55]
	64	CH_3	H	CH_3			Thalidezine	$C_{38}H_{42}N_2O_7$	158—159	+235 (chl.)	S	S	Th. fendleri [54, 56]
	65	H	CH_3	CH_3			Thalisamine	$C_{38}H_{42}N_2O_7$	191—194	−138 (chl.)	S	S	Th. simplex [54]
	66	CH_3	CH_3	CH_3			Hernandezine	$C_{39}H_{44}N_2O_7$	157—158	+250 (chl.)	S	S	Th. simplex [53, 57]
	67					$\Delta^{1',2',3',4'}$	Thalibrunimine	$C_{38}H_{40}N_2O_8$	198—200	+28 (chl.)	S	—	Th. rochebrunianum [55]
	68	CH_3					Thalibrunine	$C_{39}H_{44}N_2O_8$	172—173	+160(MeOH)	S	S	Th. rochebrunianum [58]
	69	H	H				Thalisopine	$C_{37}H_{40}N_2O_7$	215—216	−9 (EtOH)			Th. isopyroides [59—60]
	70	H	CH_3				Thalisopine	$C_{38}H_{42}N_2O_7$	151—153	−105 (ac.)	S	S	Th. isopyroides [59]
	71	CH_3	CH_3				O-Methylthalisopine	$C_{39}H_{44}N_2O_7$	163—166 (decomp.)	−54 (chl.)	S	S	Th. isopyroides [59]

TABLE 1 (continued)

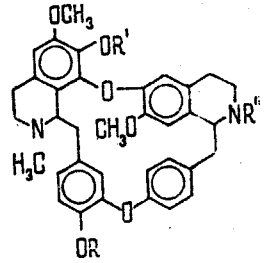
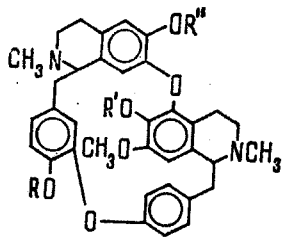
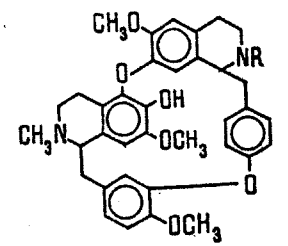
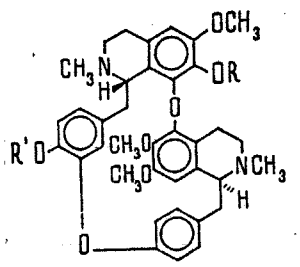
Formula	No.	R	R′	R″	R‴	R⁗	Name	Composition	mp, °C	[α]D, deg	Configuration C-1	Configuration C-1′	Source of isolation and structure
	72	H	H	CH_3			Thalicrine	$C_{36}H_{34}N_2O_6$	221–222	+341 (chl.)	S	R	Th. thunbergii [61—62]
	73	H	CH_3			$\Delta^{1',2'}$	Thalmethine	$C_{36}H_{36}N_2O_6$	275–277	+200 (chl.)	S	—	Th. minus [63—64]
	74	CH_3	H	CH_3			Homothalicrine	$C_{37}H_{40}N_2O_6$	235–236	+425 (chl.)	S	R	Th. thunbergii [61—62]
	75	H	CH_3	CH_3			Thalicberine	$C_{37}H_{40}N_2O_6$	161	+231 (chl.)	S	S	Th. thunbergii [64]
	76	CH_3	H	CH_3			Belarine	$C_{37}H_{40}N_2O_6$	158–160	−222 (chl.)	R	S	Berberis laurina [65]
	77	CH_3	CH_3			$\Delta^{1',2'}$	O-Methylthalmethine	$C_{37}H_{38}N_2O_6$	245–246	+237 (chl.)	S	—	Th. minus [63]
	78	CH_3	CH_3	CH_3			Thalmidine (O-methylthalicberine)	$C_{38}H_{42}N_2O_6$	186–187	+266 (chl.)	S	S	Th. thunbergii [66—67]
	79	CH_3	CH_3	CH_3			O-Methylisothalicberine	$C_{38}H_{42}N_2O_6$	208–209	−195 (chl.)	R	S	B. laurina [65, 68]
	80	H	CH_3	H			Dryadodaphnine	$C_{35}H_{34}N_2O_6$	—	+390 (MeOH)	S	R	Dryadodaphne novoguineensis [69]
	81	H	CH_3	CH_3			Thalictine	$C_{37}H_{40}N_2O_6$	226–228 (nitrate)	−16 (chl.)	S	S	Th. thunbergii [70]
	82	CH_3	H	CH_3			Thalmine	$C_{37}H_{40}N_2O_6$	252–253 (decomp.)	−65	S	S	Th. minus [57, 71]
	83	CH_3	H	CH_3			Lauberine	$C_{37}H_{40}N_2O_6$	250–255 (HBr)	−335 (MeOH)	R	S	B. laurina [68]
	84	CH_3	CH_3	H			Dryadine	$C_{37}H_{40}N_2O_6$	249–251 (decomp.)	+486 (chl.)	S	R	D. novoguineensis [69]
	85	H					Norpanurensine	$C_{36}H_{38}N_2O_6$	175	−250 (chl.)	R	R	Abuta panurensis [72]
	86	CH_3					Panurensine	$C_{37}H_{40}N_2O_6$	156–158	−245 (chl.)	R	R	A. panurensis [72]
	87	H	CH_3				Thalrugosidine	$C_{38}H_{42}N_2O_7$	172–174	−185 (MeOH)	S	S	Th. rugosum [39, 73]
	88	CH_3	H				Thalfetidine	$C_{38}H_{42}N_2O_7$	168–170	−89 (chl.)	S	S	Th. foetidum [74—75]
	89	CH_3	CH_3				Thaldasine	$C_{39}H_{41}N_2O_7$	105–107	−72 (chl.)	S	S	Th. rugosum [39, 73] Th. dasycarpum [75]

TABLE 1 (continued)

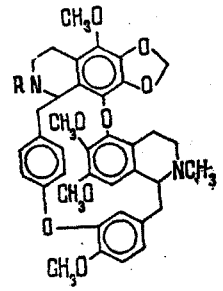
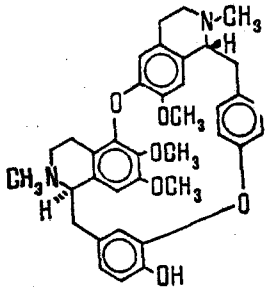
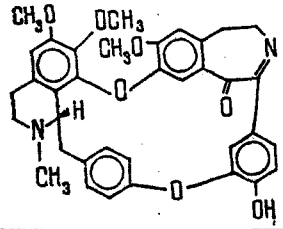
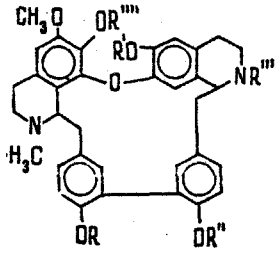
Formula	No.	R	R′	R″	R‴	R⁗	Name	Composition	mp, °C	$[\alpha]_D$, deg	Configuration C-1	Configuration C-1′	Source of isolation and structure
	90					$\Delta^{1,2,3,4}$	Thalfine	$C_{38}H_{36}N_2O_8$	148—149 (decomp.)	+69 EtOH			Th. minus [76], Th. foetidum [77]
	91	CH_3					Thalfidine	$C_{39}H_{44}N_2O_8$	117—118	+115(EtOH)			Th. foetidum [77]
	92						Nemuarine	$C_{37}H_{40}N_2O_6$	220—221	—43 (chl.)	R	R	Nemuaron vieillardii [78—79]
	93						Stepinonine	$C_{36}H_{31}N_2O_7$	244—245 or 280	—28 (Py)	S	—	Stephania japonica [80]
	94	CH_3	CH_3	H	H	CH_3	Ocotine	$C_{37}H_{40}N_2O_6$	165	+40 (chl.)			Ocotea rodiaei [19]
	95	CH_3	CH_3	H	—	CH_3 $\Delta^{1',2'}$	Ocotosine	$C_{37}H_{38}N_2O_6$	186—188	+138 (Py)			O. rodiaei [19]
	96	CH_3	H	H	CH_3	CH_3	Phlebicine	$C_{37}H_{40}N_2O_6$	195	+183 (chl.)			Crematosperma polyphlebum [81]
	97	CH_3	CH_3	H	CH_3	CH_3, N- or N′-nor	Norrodiasine	$C_{37}H_{40}N_2O_6$	282 (HCl)	+74 (H_2O)			O. rodiaei [18]
	98	H	CH_3	CH_3	CH_3	H	Tiliageine	$C_{37}H_{40}N_2O_6$	270	+138 (Py)			Tiliacora funifera [84—85]
	99	H	CH_3	CH_3	CH_3	CH_3	Funiferine	$C_{38}H_{42}N_2O_6$	218—220	+224 (chl.)			T. funifera [84—85]
	100	CH_3	CH_3	H	CH_3	CH_3	Rodiasine	$C_{38}H_{42}N_2O_6$	201—203	+147 (chl.)			O. rodiaei [18—19, 82—83]

TABLE 1 (continued)

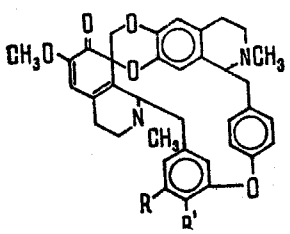
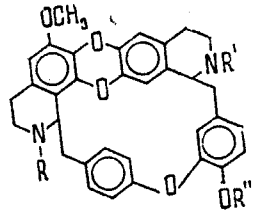
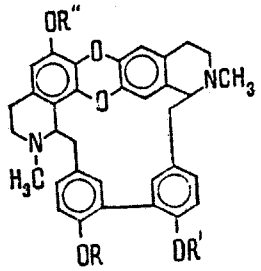
Formula	No.	R	R′	R″	R‴	R⁗	Name	Composition	mp, °C	$[\alpha]_D$, deg	Configuration C-1	Configuration C-1′	Source of isolation and structure
	101	O–CH_2–O					Repanduline	$C_{37}H_{36}N_2O_6$	215—238	+473 (chl.)			Daphnandra tenuips [86—87]
	102	$HOCH_3$					Pseudorepanduline	$C_{37}H_{38}N_2O_6$	168—173 (decomp.)	+229 (chl.)			D. sp. [88]
	103	H	CH_3	H			12-Demethyltrilobine	$C_{34}H_{32}N_2O_5$	256—258	+332 (Py)	S	S	Anisocyclea grandidieri [89]
	104	CH_3	H	H		$\Delta^{1',2'}$	1,2-Dehydromicranthine	$C_{31}H_{30}N_2O_5$	188—194 (decomp.)	−150 (chl.)	R	R	D. sp. [88]
	105	CH_3	H	H			Cocsoline	$C_{34}H_{32}N_2O_5$	195—199	+204 (chl.)	S	S	Cocculus pendulus [90]
	106	CH_3	H	H			Micranthine	$C_{31}H_{32}N_2O_5$	193—195	−231 (chl.)	R	R	D. sp. [91]
	107	H	CH_3	CH_3			Trilobine	$C_{35}H_{34}N_2O_5$	235—238	+308 (chl.)	S	S	Anisocyclea grandidieri [89]
	108	CH_3	H	CH_3			O-Methylmicranthine	$C_{35}H_{34}N_2O_5$	163—165 (decomp.)	−208 (chl.)	R	R	D. sp. [91]
	109	CH_3	H	CH_3			Telobine	$C_{35}H_{34}N_2O_5$	185—195 (decomp.)	+188 (chl.)	S	R	D. sp. [91]
	110	CH_3	CH_3	H			Cocsuline	$C_{35}H_{34}N_2O_5$	272—274	+280 (chl.)	S	S	C. pendulus [92—93]
	111		CH_3	CH_3		$\Delta^{1,2,3,4}$	Trigilletimine	$C_{35}H_{36}N_2O_5$	284 (decomp.)	−286 (CH_2Cl_2)	—	S	Triclisia gilletii [94]
	112	CH_3	CH_3	CH_3			Isotrilobine	$C_{36}H_{36}N_2O_5$	213—215	+312 (chl.)	S	S	S. hernandifolia [95], D. sp. [91]
	113	CH_3	CH_3	CH_3			O,N-Dimethylmicranthine	$C_{36}H_{36}N_2O_5$	210—214 (decomp.)	−230 (chl.)	R	R	D. sp. [91]
	114	CH_3	CH_3	H		N_a-nor	Pseudotiliarine	$C_{35}H_{34}N_2O_5$	262—268	+269 (Py)			Tiliacora funifera [96]
	115	CH_3		CH_3		R′=H or N_a-nor	Isotiliarine	$C_{35}H_{34}N_2O_5$	258—260	+195 (chl.)			T. funifera [96]
	116	CH_3	H	CH_3			Tiliarine (N-nortiliacorine	$C_{35}H_{34}N_2O_5$	203—207 (decomp.)	+283 (MeOH)			T. racemosa [97]
	117	CH_3	H	CH_3			Tiliacorine	$C_{36}H_{36}N_2O_5$	271—272	+133 (chl.)			T. racemosa [98]
	118	H	H	CH_3			Tiliacorinine	$C_{36}H_{36}N_2O_5$	195 (decomp.)	+310 (Py)			T. racemosa [97, 98]

TABLE 1 (continued)

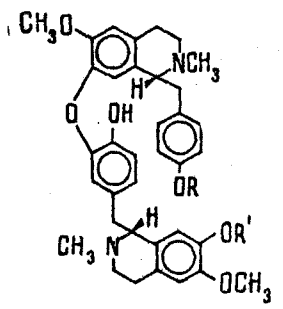
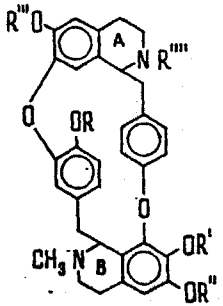
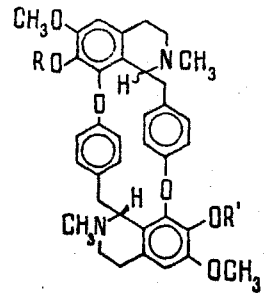
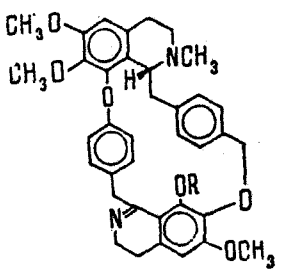
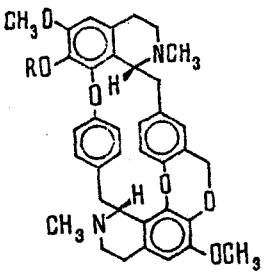
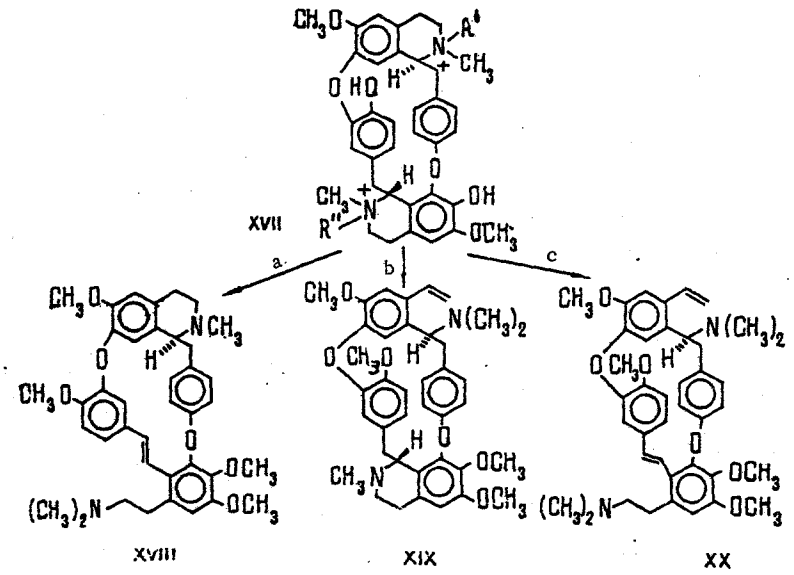
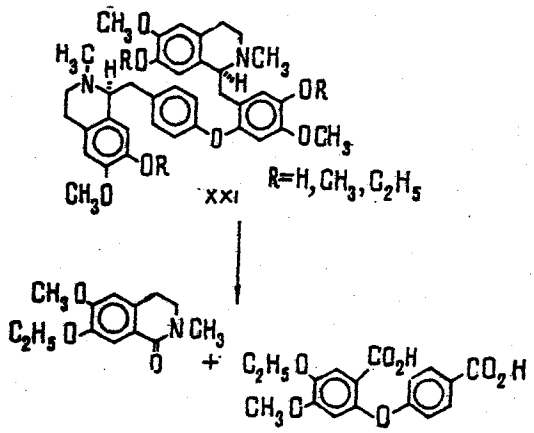
Formula	No.	R	R′	R″	R‴	R⁗	Name	Composition	mp, °C	$[\alpha]_D$, deg	Configuration C-1	Configuration C-1′	Source of isolation and structure
	119	H	CH_3				Liensinine	$C_{37}H_{42}N_2O_6$	95—99	+16 (ac.)	R	R	Nelumbo nucifera [99]
	120	CH_3	H				Isoliensinine	$C_{37}H_{42}N_2O_6$	—	+49 (ac.)	R	R	N. nucifera [100—101]
	121	CH_3	CH_3				Neferine	$C_{38}H_{44}N_2O_6$	—	—38 (chl.)	R	R	N. nucifera [100]
	122	H	H	CH_3	H	CH_3	Cycleacurine	$C_{35}H_{36}N_2O_6$	205—208	—202 (chl.)	R	R	Cyclea peltata [75]
	123	H	H	CH_3	CH_3	CH_3	d-Curine	$C_{36}H_{38}N_2O_6$	213 (220)	+331 (Py)	S	S	Ocotea rediaei [102]
	124	H	H	CH_3	CH_3	CH_3	*l*-Curine	$C_{36}H_{38}N_2O_6$	212—214 (HCl)	—276 (HCl)	R	R	Chondrodendron toxicoferum [103]
	125	H	H	CH_3	CH_3	CH_3	Hayatine (*dl*-curine)	$C_{36}H_{38}N_2O_6$	303 (decomp.)	0	RS		Cissampelos pareira [104]
	126	H	H	CH_3	CH_3	CH_3	d-Chondrocurine	$C_{36}H_{38}N_2O_6$	232—234	+173 (chl.)	S	R	Chondrodendron tomentosum [105]
	127	CH_3	H	CH_3	CH_3	CH_3	(++)-4″-O-Methylcurine	$C_{37}H_{40}N_2O_6$	164	+273 (chl.)	S	S	C. pareira [106]
	128	CH_3	H	CH_3	CH_3	CH_3	R,R-12′-O-Methylcurine	$C_{37}H_{40}N_2O_6$	162—164	—303 (chl.)	R	R	Guatteria megalophylla [107]
	129	CH_3	H	CH_3	CH_3	CH_3	Hayatidine	$C_{37}H_{40}N_2O_6$	179—180		R	S	C. pareira [106]
	130	CH_3	H	CH_3	CH_3	CH_3	Hayatinine	$C_{37}H_{40}N_2O_6$	231—232	0	RS		C. pareira [108]
	131	H	CH_3	CH_3	CH_3	CH_3	Chondrofoline	$C_{37}H_{40}N_2O_6$	135	—281 (HCl)	S	S	Chondrodendron platiphyllum [109]
	132	CH_3	CH_3	CH_3	CH_3	CH_3	R,R-Dimethylcurine, N_a HCl, N_b CH_3Cl	$C_{38}H_{42}N_2O_6$	133—136		R	R	Guatteria megalophylla [107]
	133	H	H	CH_3	CH_3	H	d-Tubocurarine, N-2 CH_3Cl	$C_{38}H_{42}N_2O_6Cl_2$	—	+215 (H_2O)	S	R	Ch. tomentosum [105, 110]
	134	H	H	CH_3	CH_3	CH_3	d-Chondrocurarine	$C_{38}H_{44}N_2O_6Cl_2$	—	+150 (H_2O)	S	R	Ch. tomentosum [105]
	135	H	H				Isochondodendrine	$C_{36}H_{38}N_2O_6$	316	—290 (chl.)	R	R	Heracleum wallichii [111]
	136	H	CH_3				Norcycleanine	$C_{37}H_{40}N_2O_6$	249—251	—27 (MeOH)	R	R	Epinetrum cordifolium [112]
	137	H	CH_3				Sciadenine	$C_{37}H_{40}N_2O_6$	254—256 (разл.)	+15 (chl.)	S	R	Sciadotenia toxifera [113]
	138	CH_3	CH_3				Cycleanine	$C_{37}H_{22}N_2O_6$	272—273	—15 (chl.)	R	R	Stephania glabra [114] E. cordifolium [112]

TABLE 1 (continued)

Formula	No.	R	R'	R"	R'"	R""	Name	Composition	mp, °C	$[\alpha]_D$, deg	Configuration C-1	Configuration C-1'	Source of isolation and structure
	139	H					Cissampareine	$C_{37}H_{34}N_2O_6$	239–240 (decomp.)	−111 (chl.)	R	—	Cissampelos pareira [115—116]
	140	CH_3					Warifteine	$C_{38}H_{40}N_2O_6$			R	—	C. ovalifolia [117]
	141	H					Insulanoline	$C_{37}H_{38}N_2O_6$	195	+99 (MeOH)	R	R	C. insularis [118]
	142	CH_3					Insularine	$C_{38}H_{40}N_2O_6$	231–233 (picrate)	+54 (MeOH)	R	R	Paracyclea ochiaiana [119]

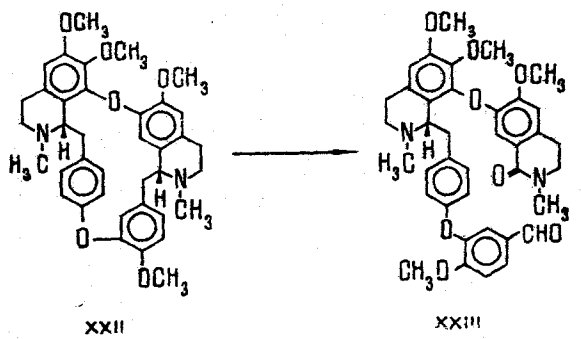


The potassium permanganate oxidation of the benzylisoquinoline bases leads to cleavage of a C–C bond with the formation of the corresponding aromatic acids and tetrahydroisoquinolines. This is the way in which, for example, the position of the methoxy group in the benzyl part of the magnolamine molecule (XXI, R = H) was established [12].

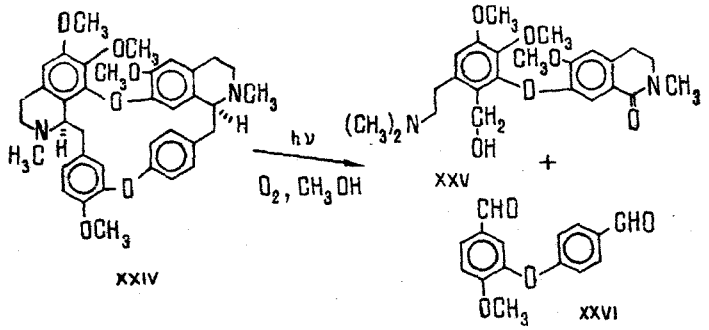


As a number of examples shows, controlled oxidation with potassium permanganate leads to the cleavage of only one C–C bond in the isoquinoline nucleus unsubstituted in the C-8 position [132]. This observation has proved to be extremely useful in establishing the structure of bisbenzylisoquinoline alkaloids such as tiliacorine [80].

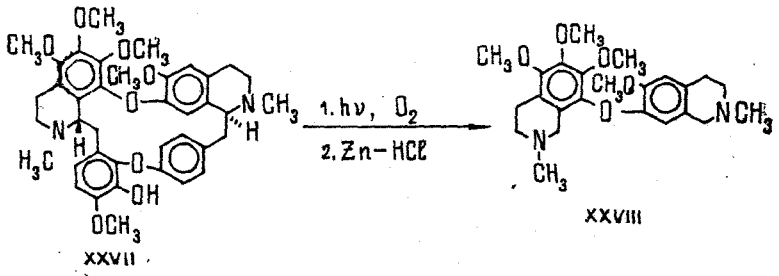
By this method it has been possible to oxidize O-methyloxyacanthine (obaberline) (XXII) to O-methylbaluchistanamine (XXIII) with a yield of 35%. Under these conditions, oxyacanthine itself is converted into baluchistanamine with a yield of only 5% [125].



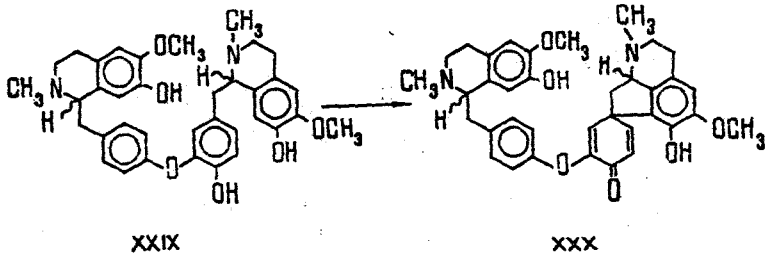
The photochemical oxidation of isotetrandrine (XXIV) forms the amino alcohol (XXV) and 4-formylphenyl 5-formyl-2-methoxyphenyl ether (XXVI) with yields of 30% and 50%, respectively [133].



Other bisbenzylisoquinoline alkaloids undergo oxidation similarly. It is convenient to isolate the nitrogen-containing component in the form of the tetrahydro derivative (XXVIII), obtained by the reduction of the oxidation products, as reported for the alkaloid thalibrunine (XXVII) [58].

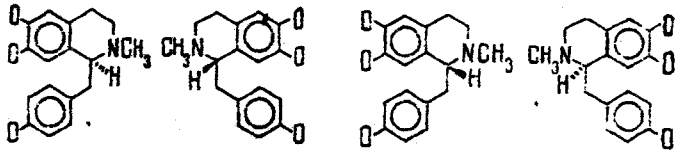


The oxidation of phenol-containing alkaloids with potassium ferricyanide leads not to the cleavage of carbon-carbon bonds but only to intramolecular oxidative condensations. On oxidation by this reagent, dl-magnoline (XXIX) is converted into the phenolic analog of dl-pakistanamine (XXX). The reaction was performed in the presence of ammonium acetate in a nitrogen atmosphere [134].



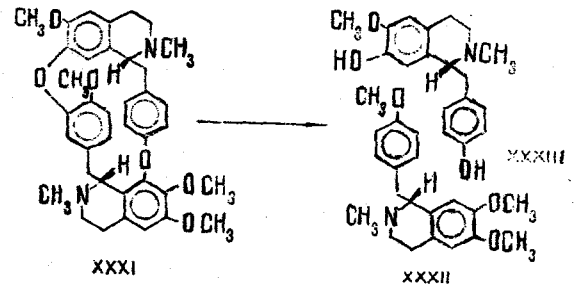
In order to determine the constitution, structure, and stereoconfiguration of the bisbenzylisoquinoline alkaloids wide use is made of the method of cleaving the diaryl ether bond with sodium in liquid ammonia. Phenolic bases are previously O-methylated or O-ethylated and are then subjected to reductive cleavage. In the final account, two benzyl tetrahydroisoquinoline fragments of the alkaloid with known structures and configurations (one phenolic, and the other nonphenolic), in which the centers of asymmetry remain unaffected, are obtained. In some cases, a mixture of several components is formed, and these can be separated chromatographically. The method is convenient because it provides the possibility of determining the configurations at the centers of asymmetry when only small amounts of the alkaloid are available.

Since the absolute configuration of the *l*-benzyltetrahydroisoquinolines has been determined accurately, the configurations of the fragments can easily be determined by direct comparison with known samples or by comparing the optical rotatory dispersion or circular dichroism curves. In view of this, the method mention may be regarded as a method of determining the absolute configurations of the bisbenzylisoquinoline alkaloid The levorotatory fragments formed on degradation correspond to the D or R configuration, and the dextrorotatory fragments to the L or S configuration:



(+)≡L≡S (−)≡D≡R

By this method, O,O-dimethylcurine (XXXI) has been converted into nonphenolic (XXXII) and phenolic (XXIII) bases, both levorotatory. The nonphenolic component was converted by the action of methyl iodide into R-O-methylarmepavine methiodide. The phenolic base was also converted into the latter compound after O-methylation and treatment with methyl iodide. Thus, both centers of asymmetry in curine have the R configuration [135]



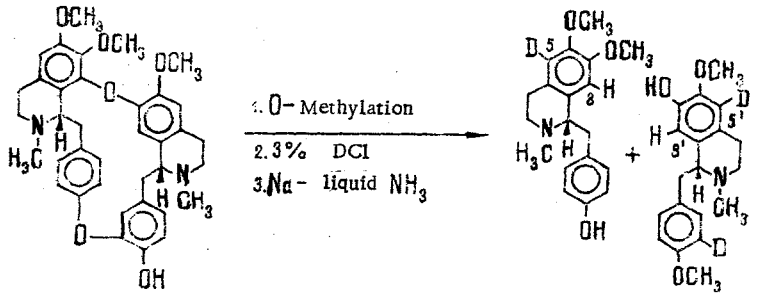
XXXI XXXII XXXIII

In the determination of the configuration of pheanthine, O,O-dimethylcurine, and O,O-dimethylisochondodendrine (cycleanine) it was found that the direction of cleavage depends on the solvent used. Thus, for example, in solution in benzene and toluene, pheanthine and O,O-dimethylcurine, on reduction with sodium in liquid ammonia, form only R-O-methylarmepavine and R-O-methylcoclaurine, while in dioxane solution pheanthine is reduced to corpaverine and laudanidine, while O,O-dimethylcurine (XXXI) gives R-laudanidine, apart from the normal cleavage products. Under the conditions mentioned, O,O-dimethylisochondodendrine forms only R-armepavine [136]. This finding considerably broadens the possibilities of the method; for example, the study of the minor byproducts of cleavage by sodium in liquid ammonia has enabled the position of the ether bond in thalidasine to be established correctly as 8−5' [75].

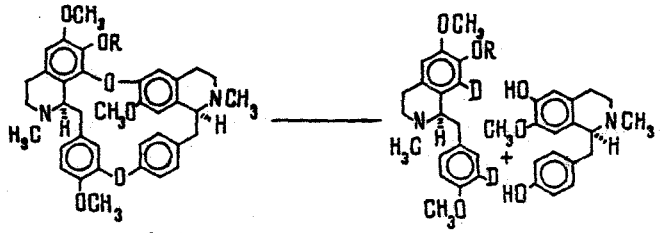
The absolute configurations of the majority of bisbenzylisoquinoline alkaloids given in Table 1 have been established by the method of cleavage with sodium in liquid ammonia. With O-methylberbamine as an example, it has been shown that the reaction takes place in two stages. After the occurrence of the first stage of cleavage with the rupture of the 8−7' ether bond, product identified as O-methylberbamunine was isolated [137].

It must be observed that the reduction of bisbenzylisoquinoline alkaloids by this method is a process that is in essence the reverse of the biosynthetic route of the oxidative coupling of benzylisoquinoline units to form bimolecular alkaloids.

The position of linkage of the diphenyl ether bridge in alkaloids of the oxyacanthine-berbamine type at C-5 or C-8 cannot be determined unambiguously by cleavage with sodium in liquid ammonia. To solve this problem it has been proposed first to carry out deuterium exchange of the methylated derivative of the alkaloid by heating at 120°C for several days with 3% DCl in D_2O and then to carry out cleavage with sodium in liquid ammonia. It can be seen from the experimental results that only the protons in ortho positions to methoxy groups are replaced by deuterium, from which it follows that the diphenyl ether bond is located at C-8 in the left-hand half of the oxyacanthine molecule [139].

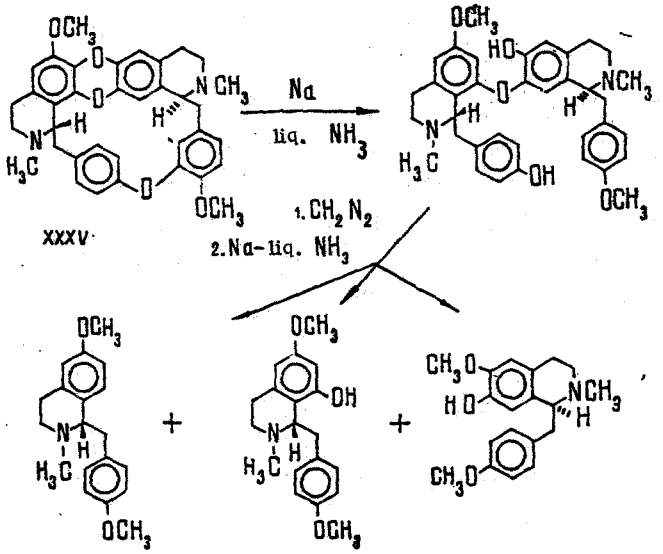


In the determination of the structure of the alkaloid (−)-belarine (XXXIV), the position of the diphenyl ether bond was determined from the position of the deuterium in the fragments after cleavage with sodium in liquid ND_3 [65].



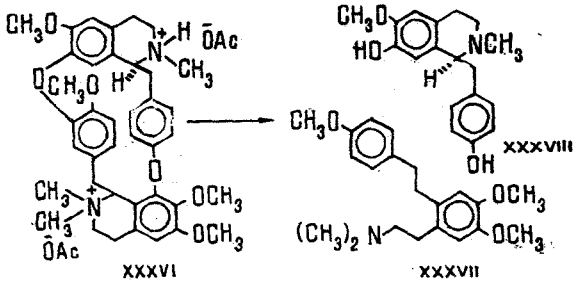
XXXIV R=H

If the molecule of a bisbenzylisoquinoline alkaloid contains a diphenylenedioxim link as, for example, in (+)-isotrilobine (XXXV), it is recommended to carry out a two-stage reductive cleavage [95].



XXXV

The cleavage of quaternary ammonium salts with sodium in liquid ammonia is accompanied by the opening of the isoquinoline nucleus. In this way it has been possible to establish a monoquaternary structure for the alkaloid tubocurarine. On cleavage by this method, the diacetate of its dimethyl ether (XXXVI) forms the β-phenylethylamine (XXXVII) and S-N-methylcoclaurine (XXXVIII) [105].



XXXVI XXXVII XXXVIII

Under similar conditions, isotetrandrine dimethiodide forms correspondingly two hydromethines, coclaurine derivatives, and armepavine [139].

Chemical methods of degradation in combination with spectral methods give the maximum amount of required information, which permits the fine structure of a compound under investigation to be established in a short time.

X-Ray structural analysis enables the spatial structure of the molecule of a bisbenzylisoquinoline alkaloid as a whole to be determined as for example, for d-tubocurarine chloride [140], and this is impossible to do by other methods. The conformation of the antitumoral alkaloid tetrandrine has been studied in the same way [141].

Additional information in the choice of alternative structures can be obtained on the basis of biogenetic considerations.

UV and IR Spectra of the Bisbenylisoquinoline Alkaloids

Like the monomeric bases [142], the bisbenzylisoquinoline alkaloids have UV spectra with an absorption maximum at ~283 nm ($\log \varepsilon$ 3.7) and a minimum at ~260 nm ($\log \varepsilon$ 3.45). Strong absorption is also observed in the 225 nm region. The UV spectra of individual groups of bisbenzylisoquinoline bases differ little. The unusual bisbenzylisoquinoline alkaloid repanduline with a spirodienone grouping absorbs at 283 and 326 nm [143].

IR spectra, in combination with other methods, provide useful information on the structure of bisbenzylisoquinoline alkaloids, particularly when they contain characteristic functional groupings such as carbonyl, hydroxy, and imino groups. However, in a number of cases they do not give sufficient information for the identification of individual representatives of bases of this type. For example, the spectra of berbamine and oxyacanthine, which are structural isomers, are indistinguishible from one another [144].

Optical Rotatory Dispersion and Circular Dichroism of the Bisbenzylisoquinoline Alkaloids

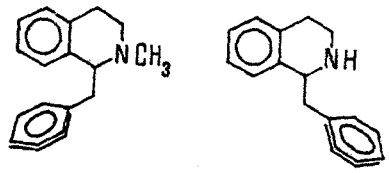
A complex Cotton effect with 3-5 extrema in the 300-220 nm region is characteristic for the optical rotatory dispersion (ORD) curves of the bisbenzylisoquinoline alkaloids. In the majority of them, a Cotton effect is observed at 290-270 nm and the first extremum of a second Cotton effect at 235 nm. No rule of optical superposition is observed for them, since not only the centers of asymmetry but also the assymetry of the molecule as a whole contributes to the optical rotation [145, 128].

The ORD curves of bases with the S,R configuration of the oxyacanthine series (type 1: 8, 7' : 11', 12-ether bonds) have two positive Cotton effects similar to the S,S bases of the tetrandrine series (type 2: 8, 7' : 12'-ether bonds), and also to the S,R bases of the curine series (type 3: 7, 11' : 8', 12-ether bonds) and differ only by the ratio of the peak magnitudes, their value decreasing in the sequence 2 > 1 > 3. The R,R bases of types 2 and 3 have ORD curves of the opposite nature. In the S,S bases of type 1 there are likewise two positive Cotton effects, the first of them is present in the negative region with shoulders at about 290 and 277 nm; there are also small maxima and minima at about 270 and 250 nm and the first extremum of a second large Cotton effect is found at 240 nm. On the other hand, in the R,S bases of type 2 a small extremum is observed between two main Cotton effects of the same size.

Proton Magnetic Resonance Spectra of the Bisbenzylisoquinoline Alkaloids

In the PMR spectra of bases of the N-methylcoclaurine type and related compounds, the protons of the methoxy groups in the 6, 7, and 4' positions have chemical shifts (τ) of 6.45-6.49, 6.23-6.25, and 6.18-6.20 ppm, respectively, which has been explained on the basis of a comparison with the spectra of the corresponding ethoxy derivatives [146]. The difference in the positions of the protons of the methoxy and ethoxy groups in the spectra is connected with the diamagnetic anisotropy of the benzene rings. A substituent at C-8 has a difinite steric effect on the conformational position of the benzene residue, which approaches the methylimino group, causing a diamagnetic effect that is reflected in a shift of the signals of the N-methyl groups by 0.1-0.18 ppm. This is also brought about by a voluminous 7-alkoxy group, since the influence of substituents in positions 6 and 4' is insignificant.

The results of a study of the PMR spectra of coclaurine derivatives [146, 147] has shown that in the tertiary and quaternary bases conformation *a* is preferred in which the benzyl group is located below the benzene ring of the tetrahydroisoquinoline part of the molecule, thereby causing an upfield shift of the signal of the proton at C-8 relative to the signal of the proton at C-5 by 0.52 ppm and of the signal of the methoxy group at C-7 in relation to that at C-6 by 0.32 ppm. Such shifts are not observed in the secondary bases, in which conformation b predominates [146-148].



a b

Conformations of *l*-benzyl-1,2,3,4-tetrahydroisoquinoline derivatives.

In the quaternary bases, the two N-methyl groups are magnetically nonequivalent, in view of which they appear in the PMR spectra in the form of well resolved signals with a distance between the peaks of ~0.25 ppm. The tetrahydroisoquinoline nucleus in these compounds has a half-chair conformation in which the benzyl group is quasiequatorial.

The rules found permit successful correlations to be made between the chemical shifts of the known functional groups and structure and stereochemistry of the bisbenzylisoquinoline alkaloids [140, 149]. However, stereochemical deviations are not always accurately predictable. They relate mainly to the chemical shifts of methoxy and methylimino groups for alkaloids of the oxyacanthine-berbamine group.

In the repandine-oxyacanthine and berbamine-tetrandrine types of alkaloids, the signals of the protons of the C-4" methoxy groups are in a weaker field (6.05-6.13 ppm) as compared with the mean value of 6.2 ppm (τ scale) for anisole, while the same group in the C-7 position gives a signal at 6.80-6.98 ppm, which is explained by the influence of the aromatic ring of the neighboring isoquinoline nucleus. The positions of the signals of the protons of methoxy groups at C-6 and C-6' vary within enormously wide limits. While the signal of the C_6-OCH_3 group is located in a weaker field (6.25 ppm) [150], the signal of a $C_{6'}-OCH_3$ group is close to that of the C_7-OCH_3 group because of the screening influence of ring B and depends on the stereoconfiguration of the molecule. It is 6.4 ppm when the configurations of the asymmetric centers are different and 6.65 ppm when they are the same. In alkaloids of the repandine type the signals of the two methylimino groups fuse into one (7.45 ppm), while in bases of the berbamine type they give two well-defined peaks at 7.4 and 7.7 ppm. The upfield shift of one signal is due to the fact that one of the methyl groups in the alkaloids of the berbamine type is close to the aromatic ring of the benzyl group.

In molecules of the isochondodendrine type, the signals of the protons of methoxy groups at C-6 and C-6' are shifted downfield (6.07-6.25 ppm) relative to the usual position, and the signals of methoxy groups at C-7 and C-7' are found in a stronger field (6.65 ppm). In the curine-chondocurine type of molecules, they differ only slightly from their normal values (6.18-6.65 ppm).

The NMR spectrum of tubocurarine chloride taken in the presence of NaOD showed the signals of the $N-CH_3$ and $N(CH_3)_2^+$ groups shifted by 56 Hz, thus confirming the monoquaternary nature of the alkaloid [105].

In alkaloids with a 5-7' ether bond, because of the less strained 21-membered macrocyclic ring the signals of the protons of the methoxy group at C-7 are close to their normal positions, and both signals of the protons at C-8 and C-8' of the isoquinoline fragment are present in the strong field because of screening by the other aromatic rings [151].

Additional information can be obtained by the deuterium exchange of protons adjacent to the hydroxy group in the presence of acids.

Mass Spectra of the Bisbenzylisoquinoline Alkaloids

Much work has been carried out on the systematization of the mass spectra of the bisbenzylisoquinoline alkaloids. For *l*-benzylisoquinoline derivatives, it has been shown that in them beta-cleavage with respect to the nitrogen atom with the elimination of the benzyl group and the formation of the strong peak of a substituted isoquinolinium ion is predominating [152, 153].

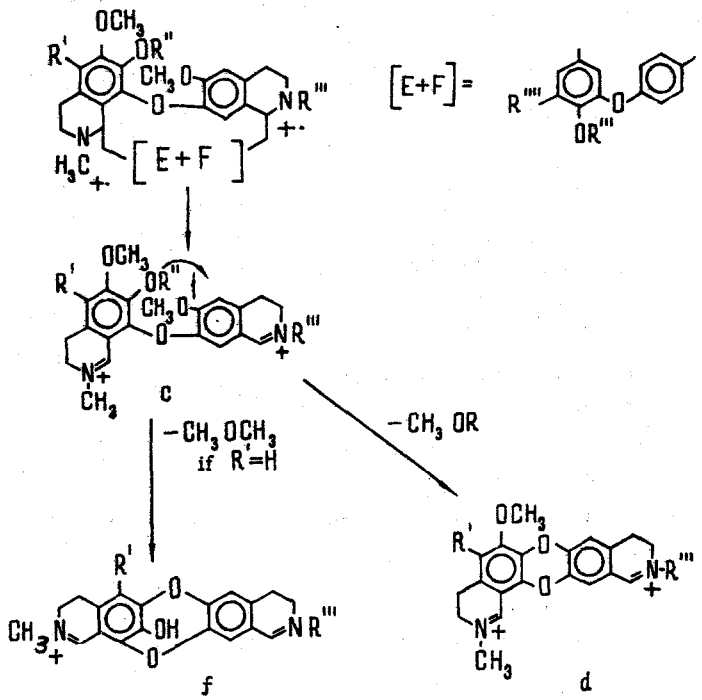
Mass spectrometry has also proved to be a convenient instrument in the structural study of the bisbenzylisoquinoline alkaloids [154-166]. Apart from the rules relating to a simple benzylisoquinolines, features of formation of fragmentary ions of low intensity connected with structural characteristics of the alkaloids are observed which enable the type of ether bond to be deduced.

Monoether alkaloids attached "tail to tail" by a 3"-4"' ether bond (type A, dauricine, magnoline, etc.), because of the most favorable benzyl cleavage, give very weak molecular ions (0.1%). The strongest ions a

those formed from rings A–B and C–D (m/e 206 and 192 for daurinoline). The subsequent fragmentation of these ions takes place to only a small extent. The splitting off of these rings in the form of neutral fragments is observed, but takes place to only a very small extent (0.1-0.2%). Stereoisomers have practically identical mass spectra.

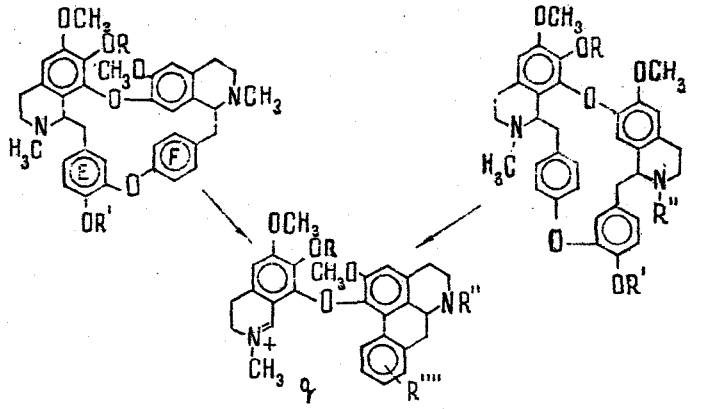
In the mass spectra of diether alkaloids of type B, having an additional 8–7' ether bond, intense singly-charged molecular ions are observed (45-100%), but doubly-charged molecular ions are usually very weak (1-3%). The doubly charged ions c arising on double benzyl cleavage are, as a rule, the main peaks in the spectra of alkaloids of this type.

On the basis of the results of a study of the mass spectra of deuterated compounds it has been possible to determine the mechanisms of fragmentation of the alkaloid molecules during mass spectrometry, to elucidate the nature of the weak ions, and also to determine the nature and position of the substitutents in the aromatic rings.



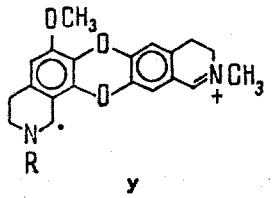
Characteristic for ion c is the splitting off of dimethyl ether with the formation of an ion with a dibenzo-1, 4-dioxin structure d. If there is a hydroxy group in position C-7 of the alkaloid (R" = H), the formation of dimethyl ether takes place at the expense of the methoxy group at C-6 with subsequent rearrangement of the ion f into the less strained structure d. No splitting off of dimethyl ether is observed for the ion c with m/e 190 in the mass spectrometry of the alkaloid cepharanthine having a methylenedioxy group in the 6–7 position.

In alkaloids of this type weak but fairly reproducible ions (2-8%) connected with the splitting out of ring E and the formation of the aporphine system q are also observed, and this enables the nature of the substituents in ring E to be determined.



For the mass spectra of the dehydrobisbenzylisoquinoline alkaloids of this series – for example, stebisimine and epistephanine – one strong singly charged molecular ion (100%), and also the corresponding doubly-charged molecular ion (13%) are characteristic because of hindered benzyl cleavage.

Alkaloids with three ether bonds (type C), which include trilobine and iostrilobine, undergo a double benzyl cleavage with the formation of a doubly charged ion x, identical with ion d of the alkaloids of group B, and the singly charged ion y, the latter, unlike the former, undergoing further fragmentation with the loss of H• and Me•

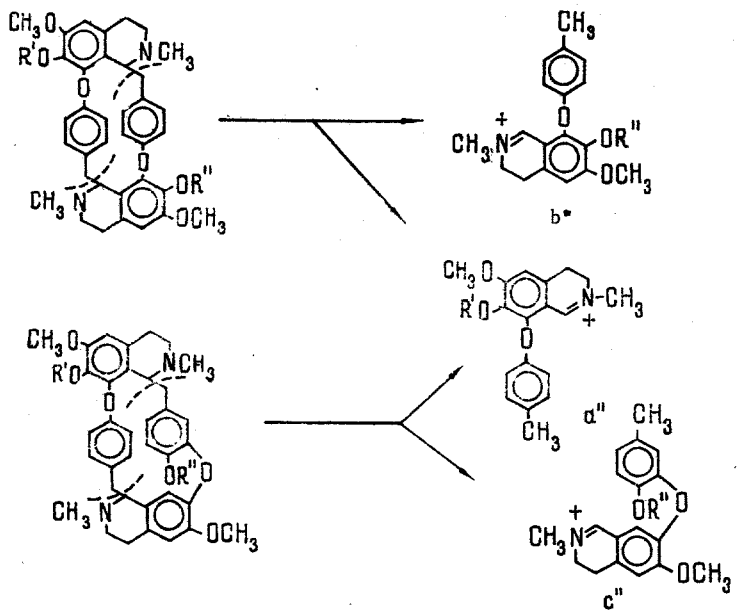


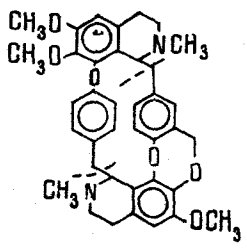
y

The mass spectra of thalmine and its derivatives with 5–7' ether bonds are similar to those of the alkaloids with the 8–7' ether bonds. The direction of fragmentation of the main ion o formed on double benzyl cleavage of the doubly charged molecular ion depends on the nature of the substituents R' and R", which makes it possible to fix the position of the substituents in the isoquinoline nuclei [166].

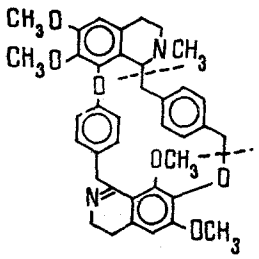
The mass spectra of thalicberine and of other alkaloids with a 8–6' bonds resemble those of alkaloids of type B, except for the absence of the ions M – 191, M – 192, M – 177, and M – 178. For the alkaloid thalidasine with an 8–5' ether bond the loss of ring E is characteristic.

The mass spectra of compounds of the isochondodendrine series (type H) and of the curine series (type I) have been considered in a number of publications [154, 156, 164, 165). Characteristic for them is benzyl cleavage to form the corresponding $a''-b''$ and $a''-c''$ fragments with migration of a hydrogen ion. When R' = R", alkaloids of types H and I give one ion (100%) in which a'' is identical with the ion b", and the ions a'' and c" are isomeric. Where the substituents are different, the two types of ions expected are observed. The ions formed on double benzyl cleavage without the migration of hydrogen are weaker, being predisposed to further fragmentation.





XXXIX



XL

The cleavage of the alkaloid insularine (XXXIX) takes place in the usual way characteristic for alkaloids of the H-I type [166]. Warifteine (XL) differs from the alkaloids considered by the presence of its p-xylyl residue. Since the normal fragmentation pathway is suppressed by the imine bond, the fragment M – C_8H_8 forms the main peak [115].

Biological Activity of the Bisbenzylisoquinoline Alkaloids

The main action of quaternary bisbenzylisoquinoline derivatives is expressed in a lowering of the tonus of the cross-striated muscles, to the extent of the complete paralysis. They are well known in medicine as muscle relaxants. d-Tubocurarine chloride, which has found use in surgical practice, blocks nerve-muscle transfer by interacting with the acetylcholine receptors. It causes a weakening of the skeletal musculature and is used to supplement narcosis in complex surgical operations, for treating various disturbances of muscular activity, and also in psychiatric practice – the shock treatment of schizophrenia [167, 168]. The activity of the bisquaternary derivatives depends on the type of base, the substituents, and the stereochemistry of the alkaloids. For example, chondocurarine chloride is three times more active than d-tubocurarine chloride, and the antipode of the latter – *l*-tubocurarine chloride – is ten times weaker than d-tubocurarine chloride [169-171].

Methylation of the phenolic hydroxyls in tubocurarine chloride leads to an enhancement of the curare activity [171, 172] but ethylation or butylation lowers the activity and even leads to its disappearance [172]. The tertiary bases possess a weak curaremimetic activity or are completely free from it. The tertiary bases tetrandrine, cycleanine, thalsimine, dihydrothalsimine hernandezine, thalmine, thalictrinine, and fetidine possess antiinflammatory properties, while the majority of compounds are 2-4 times more active than amidopyrine and sodium salicylate [173-176]. Replacement of a methyl group attached to a nitrogen atom by an acetyl group sharply decreases the activity of such compounds.

The alkaloids magnoline, magnolamine, and oxyacanthine are characterized by a strong depressive action [177-179]. Antitubercular activity has been found for cepharanthine, isotetrandrine, trilobine, and tetradrine [180-186], and antitumoral activity in O-methyldauricine, tetrandrine, thalmine, halidasine, cocculinine, pheanthine, and other alkaloids [49, 187-191].

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