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Berberis ALKALOIDS

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This review systematizes literature information on alkaloids of plants of the genus Berberis. *The main chemical and spectral methods of establishing their structures, and also their pharmacological properties, are considered. The review includes literature sources up to 1992.*

Plants of the genus *Berberis* L. (family Berberidaceae) are some of the most widely distributed on the terresterial globe. Their name originates from the locality Barbary (Africa). Information on the number of species is extemely contradictory: from 100 to 700 [1-5]. On the territory of the CIS, the main floristic varieties concentrated in Central Asia — 9 species — while 3 species are found in the Causasus and one species each in Siberia and the Far East.

The use of barberries in medicine has been known from remote antiquity. Thus, in inscriptions on clay tablets in the library of the Assyrian emperor Asurbanipal from 650 BC the fruit of the barberry is mentioned as a blood-purifying agent [4]. The great physician of the Middle Ages Abu' Ali Ibn Sina (Avicenna) used in his practice barberry fruit, leaves, and roots for the preparation of drugs against hepatic and gastrointestinal diseases and also against diseases of the gall bladder and the spleen [6]. There is information on the use of various organs of *B. vulgaris* L. and the alkaloid berberine for the treatment of malignant neoplasms: for liver tumors and cancer of the stomach and throat [7, 8, 31]. In Central Asia, decoctions of barberry roots or the bark of the roots are used for the treatment of bone fractures, dislocations, strains, wounds, and burns [10].

All species of *Berberis* are typical alkaloid-bearing plants [11]. The study of the alkaoids of these plants was begun as early as 1837 by Buchner and Herberger [12]: from the roots of *B. vulgaris* L. they isolated a yellow crystalline base which they called berberine. However, this alkaloid had been isolated previously, in 1826, by Chevalier and Pelletan from the bark of *Xanthoxylon clava Herculis* [13]. Berberine belongs to the diisoquinoline alkaloids and is widely distributed in the vegetable kingdom. It is one of the first alkaloids that found use in medicine. Its production was begun at the beginning of the XXth century in Germany [14], and its chemical structure was established by Perkin [15]. Later he achieved its total synthesis [16].

Berberine is present in all the *Berberis* species studied (Table 2). It can be detected in the leaves, flowers, fruit, young shoots, stems, and roots. The maximum accumulation of the alkaloid is observed in the roots of the plant in the fruit-ripening period [11]. In our country, berberine is used in medicine as a cholagogue. The roots of *B. vulgaris* are used as the raw material source for the production of berberine [9, 11, 19].

A number of review papers have been devoted to the chemistry and pharmacology of the *Berberis* alkaloids [17, 31, 33]. In them, the main attention has been devoted to pharmacology, and the spectral and chemical properties of the alkaloids have been considered inadequately. About 20 years have passed since the last of them was published. During this period many new alkaloids have been isolated from barberries, among which there are bases with unusual types of structure (Table 3).

The present review covers the literature on *Berberis* alkaloids up to 1992, and lists of the species of *Berberis* investigated and the alkaloids isolated from them are given. The basic chemical and spectral methods of proving the structures of the *Berberis* alkaloids and their pharmacological properties are considered.

Up to the present time, the alkaloids of about 80 *Berberis* species have been investigated and 129 alkaloids have been isolated (Table 1). They belong to 16 types of isoquinoline bases (Table 3).

Table 2 gives the species investigated and the structure numbers of the alkaloids isolated, which correspond to Tables 1 and 3.

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TABLE 1. Alkaloids of Plants of the Genus *Berberis*

Alkaloids	Composition	Structure	mp, °C	$[\alpha]_D$, deg	Literature
1	2	3	4	5	6
I. PROTOBERBERINE ALKALOIDS					
1. Berberine	$C_{20}H_{18}O_4N^+$	1	144	—	21, 116
2. Palmatine	$C_{21}H_{22}O_4N^+$	4	Iodide 262 Chloride 205—206	—	21, 116
3. Columbamine	$C_{20}H_{20}O_4N^+$	3	Chloride 239—240	—	21, 116
4. Jatrorrhizine	$C_{20}H_{20}O_4N^+$	2	Chloride 205—208	—	21, 116
5. Berberrubine	$C_{19}H_{16}O_4N^+$	6	285	—	21, 116
6. Epiberberine	$C_{20}H_{18}O_4N^+$	5	Iodide 300	—	21
7. Dehydrocorydaline	$C_{22}H_{24}O_4N^+$	7	Iodide 245—246	—	21
8. Thalifendine	$C_{19}H_{16}O_4N^+$	8	Chloride 230	—	21
9. 8-Oxoberberine (berlambine)	$C_{20}H_{17}O_5N$	14	199—200	—	101
10. Dihydroberberine (lambertine)	$C_{20}H_{19}O_4N$	18	164	—	101
11. 8-Oxopalmatine	$C_{21}H_{21}O_5N$	16	240—241	—	25
12. Dihydropalmatine	$C_{21}H_{23}O_4N$	19	168—169	—	58
13. Dihydropalmatine N-oxide	$C_{21}H_{23}O_5N$	19a	166—168 (decomp.)	—	57
14. *l*-Tetrahydropalmitine	$C_{21}H_{25}O_4N$	10	141	—278 (C_2H_5OH)	96
15. N-Methyldihydroberberine	$C_{21}H_{22}O_4N^+$	20	210—212	—	128
16. 8-Oxoberberrubine	$C_{19}H_{15}O_5N$	15	250—251	—	128
17. Pseudopalmitine	$C_{21}H_{22}O_4N^+$	23	Chloride 212—213	—	128
18. *l*-Tetrahydroberberine	$C_{20}H_{21}O_4N$	9	133—134	—292 (CH_3OH)	127
19. *l*-Tetrahydroberberrubine	$C_{19}H_{19}O_4N$	11	188—190	—287 (C_2H_5OH)	130
20. Cyclanoline	$C_{20}H_{24}O_4N^+$	22	Chloride 214—215	—115 (CH_3OH)	21
21. Corydaline	$C_{22}H_{27}O_4N$	12	135—136	—	31
22. (±)-Thalictricavine	$C_{21}H_{23}O_4$	13	211—212	±0 ($CHCl_3$)	130
23. (+)-β-N-Methylcorypalmine	$C_{21}H_{26}O_4N^+$	21	Iodide 230—231	+127 (CH_3OH)	131
24. O-Methylprechilenine	$C_{21}H_{19}O_7N$	25	Amorph.	—	25
25. Prepseudopalmanine	$C_{21}H_{21}O_7N$	26	Amorph.	—	25
26. 13-Methoxyoxoberberine	$C_{21}H_{19}O_8N$	17	197—200	—	25
27. Karachine	$C_{25}H_{27}NO_5$	27	146—148	—	35
28. Valachine	$C_{25}H_{25}O_5N$	28	237—238	—	119
29. Berberastine	$C_{20}H_{17}O_5N^+$	24	132—137	+107 (C_2H_5OH)	95
II. BISBENZYLISOQUINOLINES (BBIQs)					
30. Berbamunine	$C_{36}H_{40}O_6N_2$	29	190—191	+87 (CH_3OH)	82
31. 2′-Norbermunine	$C_{35}H_{38}O_6N_2$	32	Amorph.		112
32. Espinine	$C_{36}H_{40}O_6N_2$	30	123—125	+25 ($CHCl_3$)	129
33. Espinidine	$C_{37}H_{42}O_6N_2$	31	Amorph.	+31 ($CHCl_3$)	129
34. Chilenamine	$C_{37}H_{42}O_7N_2$	34	—*		26
35. Temuconine	$C_{37}H_{42}O_6N_2$	33	—*	+77 (CH_3OH)	123
36. Oxyacanthine	$C_{37}H_{40}O_6N_2$	35	216—217	+285 ($CHCl_3$)	31
37. Berbamine	$C_{37}H_{40}O_6N_2$	44	156	+109 ($CHCl_3$)	31
38. Obaberine	$C_{38}H_{42}O_6N_2$	36	139—140	+634 ($CHCl_3$)	44
39. Isotetrandrine	$C_{38}H_{42}O_6N_2$	45	180—182	+161 ($CHCl_3$)	44
40. Baluchistine	$C_{36}H_{38}O_6N_2$	41	222—224	+333	41
41. Aromoline	$C_{36}H_{38}O_6N_2$	37	198—202	+249 (C_5H_5)	44

TABLE 1. (Continued)

1	2	3	4	5	6
42. Homoaromoline	$C_{37}H_{40}O_6N_2$	38	235—236	+425 ($CHCl_3$)	44
43. Obamegine	$C_{36}H_{32}O_6N_2$	46	171—173	+273 ($CHCl_3$)	44
44. Thalrugosine	$C_{37}H_{40}O_6N_2$	47	153	+87 (CH_3OH)	44
45. Berbamine 2′-β-oxide	$C_{37}H_{40}O_7N_2$		Amorph.	—	45
46. Penduline	$C_{37}H_{40}O_6N_2$	40	192—194	+265 ($CHCl_3$)	45
47. Osornine	$C_{38}H_{42}N_2O_7$	42	244—245	—151 ($CHCl_3$)	26
48. Calafatine	$C_{39}H_{44}O_7N_2$	50	135—137	+280 ($CHCl_3$)	46
49. Calafatine 2-α-N-oxide	$C_{39}H_{44}O_8N_2$	50a	Amorph.	—48 (CH_3OH)	122
50. Calafatine 2-β-N-oxide	$C_{39}H_{44}O_8N_2$	50в	Amorph.	—19 (CH_3OH)	122
51. O-Methylisothalicberine	$C_{38}H_{42}O_6N_2$	53	207—208	—297 ($CHCl_3$)	52
52. Isothalicberine	$C_{37}H_{40}O_6N_2$	54	153—155	—205 ($CHCl_3$)	52
53. 7-O-Demethylthalicberine	$C_{36}H_{38}O_6N_2$	55	245—247	—230 ($CHCl_3$)	52
54. Oblongamine	$C_{38}H_{42}O_6N_2^+$	39	Iodide 198—200	+54,5 (CH_3OH)	82
55. 2′-N-Methylberbamine	$C_{38}H_{42}O_6N_2^+$	48	Iodide Amorph.	—	159
56. 2′-N-Methylisotetrandrine	$C_{39}H_{44}O_6N_2^+$	49	Iodide 220—222	+29,2 ($CHCl_3$)	126
57. Belarine	$C_{37}H_{40}O_6N_2$	56	158—160	—222 ($CHCl_3$)	99
58. Lauberine	$C_{37}H_{40}O_6N_2$	51	2HBr 250—255	+481 ($CHCl_3$)	44
59. Berberilaurine	$C_{36}H_{38}O_6N_2$	52	—*	— (C_2H_5OH)	44
III. APORPHINE-BENZYLISOQUINOLINE DIMERS (ABIQs)					
60. Pakistanine	$C_{37}H_{40}O_5N_2$	57	154—156	+106 (CH_3OH)	43
61. O-Methylpakistanine	$C_{38}H_{42}O_5N_2$	58	—*		108
62. 2′-Norpakistanine	$C_{36}H_{38}O_6N_2$	59	148	+9,1 (CH_3OH)	121
63. Chitraline	$C_{36}H_{38}O_6N_2$	60	—*	+136 (CH_3OH)	109
64. O-Methylchitraline	$C_{37}H_{40}O_6N_2$	61	Amorph.		121
65. Porveniramine	$C_{36}H_{33}O_6N_2$	62	—*	+40 (CH_3OH)	64
66. Khyberine	$C_{36}H_{38}O_6N_2$	63	145—147	—47 (CH_3OH)	48
67. Kalashine	$C_{37}H_{40}O_6N_2$	64	—*		107
IV. PROAPORPHINE-BENZOISOQUINOLINE DIMERS (PABIQs)					
68. Pakistanamine	$C_{38}H_{42}O_6N_2$	65	HCl-215	+20 (CH_3OH)	43, 85
69. Epivaldiberine	$C_{36}H_{38}O_6N_2$	66	—*	+31 (CH_3OH)	64
70. Epiberbivaldine	$C_{36}H_{38}O_6N_2$	67	Amorph.	+45,7 ($CHCl_3$)	28, 29
71. Epivaldivianine	$C_{37}H_{40}O_6N_2$	68	—*	+69,4 (CH_3OH)	121
72. Berbivaldine	$C_{36}H_{38}O_6N_2$	69	—*	+140 (CH_3OH)	64
73. Valdiberine	$C_{36}H_{38}O_6N_2$	70	—*	+91 (CH_3OH)	64
74. Patagonine	$C_{37}H_{40}O_6N_2$	71	—*	+192 (CH_3OH)	49
75. Rupăncamine	$C_{37}H_{40}O_6N_2$	72	Amorph.	+116,9 ($CHCl_3$)	28, 29
76. Valdianine	$C_{37}H_{40}O_6N_2$	73	—*	+120 (CH_3OH)	49
V. SECO-BISBENZYLISOQUINOLINES (S-BBIQs)					
77. Jhelumine	$C_{36}H_{38}O_7N_2$	74	Amorph.	+28 (CH_3OH)	95
78. Chenabine	$C_{37}H_{40}O_7N_2$	75	Amorph.		95
79. Curacautine	$C_{39}H_{42}O_9N_2$	76	Amorph.	—5 (CH_3OH)	26
80. Talcamine	$C_{40}H_{44}O_{10}N_2$	77	Amorph.	—2 (CH_3OH)	26
81. Punjabine	$C_{35}H_{32}O_7N_2$	78	Amorph.	—40 (CH_3OH)	94
82. Gilgitine	$C_{36}H_{34}O_8N_2$	79	Amorph.		94
83. Baluchistanamine	$C_{37}H_{38}O_8N_2$	80	122—124		42
84. Sindamine	$C_{37}H_{38}O_8N_2$	81	Amorph.		94
VI. INDANOBENZAZEPINES AND RELATED ALKALOIDS					
85. Chilenine	$C_{20}H_{17}O_7N$	82	154—155		66
86. Palmanine	$C_{21}H_{21}O_7N$	83	Amorph.		25
87. 13-Desoxychilenine	$C_{20}H_{17}O_6N$	84	Amorph.	—	25
88. Lennoxamine	$C_{20}H_{19}O_5N$	85	225	—	60
89. Chilenamine	$C_{20}H_{21}O_4N$	86	—*	—	25

TABLE 1. (Continued)

1	2	3	4	5	6
90. Pictonamine	$C_{22}H_{19}O_6N$	87	228—230	—	25
91. Nuevamine	$C_{19}H_{17}O_5N$	88	212	—	60
92. Magallenesine	$C_{21}H_{17}O_6N$	89	254—256	—	59
93. Puntarenine	$C_{21}H_{19}O_6N$	90	214—216	—	22, 68
VII. BENZYLISOQUINOLINES					
94. Berbitine	$C_{19}H_{17}O_5N$	91	Amorph.	—	30
95. Taxilamine	$C_{20}H_{19}O_6N$	92	Amorph.	—	36
96. Dihydrorugosinone	$C_{19}H_{17}O_6N$	93	220—221	—	23
97. Dihydrotaxilamine	$C_{20}H_{21}O_6N$	94	Amorph.	—	30
98. Gandharamine	$C_{19}H_{18}O_4N^+$	95	Iodide 185—186	—	40
99. Polyberine	$C_{20}H_{19}O_6N$	102	Amorph.	—	120
100. Laudanosine	$C_{21}H_{27}O_4N$	96	87—88	+83 (CH_3OH)	128
101. Reticuline	$C_{19}H_{23}O_4N$	97	Amorph.	+206 (C_2H_5OH)	80
102. N-Methylcoclaurine	$C_{18}H_{21}O_3N$	98	153—154	+90,1 ($CHCl_3$)	44
103. Juziphine	$C_{18}H_{21}O_3N$	99	89—90	+8	115
104. Oblongine	$C_{19}H_{24}O_3N^+$	100	158—159	+8,5 (CH_3OH)	39, 104
105. Karakoramine	$C_{25}H_{27}O_5N$	101	—*	+71 (CH_3OH)	95
106. N-Methylarmepavine	$C_{20}H_{26}O_3N^+$	103	Amorph.	+72 (CH_3OH)	39
VIII. APORPHINES AND PROAPORPHINES					
107. Glaucine	$C_{21}H_{25}O_4N$	104	120—121	+88 (CH_3OH)	84
108. Isoboldine	$C_{19}H_{21}O_4N$	105	125—126	+57 (C_2H_5OH)	80
109. Thalicmidine	$C_{20}H_{23}O_4N$	106	191—192	+56 (CH_3OH)	84
110. Magnoflorine	$C_{20}H_{24}O_4N^+$	107	Iodide 248	+193 (CH_3OH)	82
111. Isocorydine	$C_{20}H_{23}O_4N$	108	183—184	+176 (CH_3OH)	84
112. Thalicmidine N-oxide	$C_{20}H_{23}O_5N$	106a	192—193	+90 (CH_3OH)	80
113. Isocorydine N-oxide	$C_{20}H_{23}O_5N$	108a	HCl·228—229	—	80
114. Natalinine	$C_{25}H_{23}O_5N$	109	—*	—	69
115. Coyhaiquine	$C_{25}H_{27}O_5N$	113	Amorph.	+28 (CH_3OH)	63
116. Pronuciferine	$C_{19}H_{21}O_3N$	114	127—129	+99 ($CHCl_3$)	74
117. Apoglaziovine	$C_{18}H_{19}O_3N$	110	149 (decomp.)	—35 ($CHCl_3$)	45
118. O-Methylcorydine N-oxide	$C_{21}H_{25}NO_5$	111	—*	+193 (CH_3OH)	56
119. Natalamine	$C_{25}H_{25}O_5N$	112	—	—5 (CH_3OH)	65
IX. CORYDINEMETHINE AND RELATED ALKALOIDS					
120. Corydinemethine	$C_{21}H_{25}O_4N$	115	Amorph.	—	51
121. Chiloenine	$C_{20}H_{21}O_6N$	117	Amorph.	—	24
122. Chiloenamine	$C_{20}H_{23}O_6N$	116	Amorph.	—	24
123. Andesine	$C_{20}H_{21}O_6N$	120	Amorph.	—	27
124. Aconcagunine	$C_{20}H_{23}O_6N$	118	Amorph.	—	28
125. Santiagonamine	$C_{19}H_{18}O_3N_2$	119	—*	—	151
X. QUETTAMINE AND RELATED ALKALOIDS					
126. Dihydrosecoquettamine	$C_{19}H_{23}O_3N$	121	Amorph.	—	39
127. Secoquettamine	$C_{19}H_{21}O_3N$	122	171—172	—	39
128. Quettamine	$C_{19}H_{22}O_3N^+$	123	*	—	39
XI. ISOQUINOLINE-ISOQUINOLONE DIMERS					
129. Berbidine	$C_{23}H_{28}O_5N_2$	124	Amorph.	—	150
XII. CULARINES					
130. Linaresine	$C_{19}H_{15}O_6N$	125	215	—	120
131. Dihydrolinaresine	$C_{19}H_{17}O_5N$	126	170	—	120
XIII. PAVINE GROUP					
132. Norargemonine	$C_{20}H_{23}O_4N$	127	—*	—	47
133. Argemonine	$C_{21}H_{25}O_4N$	128	152—153	+218 (C_2H_5OH)	47

TABLE 1. (Continued)

1	2	3	4	5	6
		XIV. PROTOPINE GROUP			
134. Cryptopine	$C_{21}H_{23}O_5N$	129	216—217	—	71
135. Protopine	$C_{20}H_{19}O_5N$	130	205—206	—	71, 98
		XV. SIMPLE ISOQUINOLINES			
136. Noroxohydrastinine	$C_{10}H_9O_3N$	132	184—185	—	44
137. Corydaldine	$C_{11}H_{13}O_3N$	133	175	—	43
138. Thalifoline	$C_{11}H_{13}O_3N$	134	208—211	—	44
		XVI. PHTHALIDEISOQUINOLINES			
139. *l*-β-Hydrastine	$C_{21}H_{21}O_6N$	131	132	—68 ($CHCl_3$)	31

*Melting points not given in the literature.

TABLE 2. Plants of the Genus *Berberis* Investigated and the Alkaloids Isolated

	Plant species	Alkaloids isolated	Literature
1	2	3	4
1.	B. aethnensis	1	21
2.	B. actinicantha Mart ex Shult.	25, 16, 24, 67, 72, 82, 83, 84, 91, 93, 94, 116, 117, 118, 120	22, 23, 25, 26, 27, 29, 30, 88
3.	B. amurensis Rupr.	1, 2, 4, 29, 44, 107	31, 32
4.	B. aristata DC.	1, 2, 3, 4, 27, 35, 44	33, 35, 36
5.	B. asiatica Rox.	1, 2, 3, 4, 10, 14, 35, 44	37, 38
6.	B. aquifolium	1, 35, 41	21
7.	B. auxifolia	1	31
8.	B. baluchistanica Ahrendt.	12, 35, 36, 41, 57, 65, 80, 95, 100, 103, 121, 122, 123, 133	33, 39, 40, 41, 42, 43
9.	B. buxifolia Lam.	1, 4, 34, 50, 50a, 50в, 42, 76, 77, 116, 117, 120, 128	21, 24, 26, 46, 47, 122
10.	B. brandisiana Ahrendt.	40, 44, 44a, 45, 97, 105, 110, 124, 134	45, 150
11.	B. boliviana Lechl.	1, 35, 36, 37, 38, 44, 45, 46, 47, 71, 103, 125, 126, 132, 134	44, 49
12.	B. bumeliaefolia Shneid.	1, 4, 29, 35, 37, 44, 45, 130	44
13.	B. berbeyana	1	44
14.	B. chilensis Gills ex Hook.	44, 53, 54, 55, 97	52, 53, 74
15.	B. calliobotrys	60, 63	22, 48
16.	B. carataegina DC.	1, 2, 4, 107	33
17.	B. cretica L.	1, 2, 4, 29, 35, 36, 37, 44, 45, 46, 47, 104, 105	50, 51
18.	B. coriaria Royle.	1	54
19.	B. chochoco	1	55
20.	B. chitria	1, 18, 19, 19a, 25, 35, 111	21, 56, 57, 58
21.	B. darwini Hook.	1, 14, 16, 17, 25, 61, 82, 85, 86, 87, 88, 89, 93, 119, 120, 130	21, 25, 59, 60, 74, 121, 151
22.	B. densiflora Boiss.	1	11
23.	B. empetrifolia Lam.	1, 14, 45, 57, 60, 62, 71, 73, 82, 85, 90, 109, 112, 113, 130	25, 63, 64, 66, 68, 69
24.	B. fortunei	1, 2, 4, 35, 44, 107	31
25.	B. francesciferdinandi Shneid.	1, 4, 35, 44	21, 31
26.	B. floribunda	1, 2, 3, 4, 35, 44, 77	70
27.	B. gracilis	1, 9, 129, 130	71

TABLE 2. (Continued)

1	2	3	4
28.	B. quimpelii	1, 2, 3, 4, 6, 35, 44	72
29.	B. hauniensis Zab.	1, 2, 3, 4, 6, 35, 44	73
30.	B. hakeoides	114	74
31.	B. heterobothrys E. Wolf.	1, 4	75, 76
32.	B. heteropoda Schrenk.	1, 2, 3, 4, 9, 15, 20, 23, 29, 35, 37, 44, 96, 97, 104, 107, 106, 108	76, 78, 127, 128
33.	B. himalaica	1, 2, 35, 44	77
34.	B. hakodate	1, 2, 3, 4, 6, 35, 44	77
35.	B. iberica Stev.	1, 2, 4	11
36.	B. insignis	1	21
37.	B. illiensis M. Pop	1, 2, 6, 21, 29, 44, 98, 107	81, 131
38.	B. integerrima Bge.	1, 4, 29, 35, 44, 45, 104, 105, 106, 106a, 107, 108, 108a	80, 82, 83, 84
39.	B. julianae	1, 2, 4, 35, 44, 65, 104, 107	85, 86, 87
40.	B. japonica	1, 4, 44, 45, 107	21, 59
41.	B. kaschgarica Rupr.	1	11
42.	B. kawakamii	1, 2, 44, 45, 107	89
43.	B. koreana	1—4, 28—30, 35, 37—39, 44, 46, 98	90, 91, 93
44.	B. lycium Royle.	1, 4, 14, 29, 35, 44, 74, 75, 78, 79, 81, 101	92, 93, 94, 95
45.	B. laurina Billbg.	1, 4, 10, 24, 30, 31, 35, 37, 38, 47, 53, 55, 56, 51, 52, 130, 131	44, 97, 98, 99, 100, 129
46.	B. lamberti Parker.	1, 2, 3, 4, 14, 35, 44	101
47.	B. mingetsensis	1, 2, 14, 44, 45, 107	89
48.	B. morrionensis	1, 2, 14, 44, 45, 107	33, 90
49.	B. nummularia Bge.	1, 2, 3, 4, 9, 13, 29, 35, 106, 107, 108	83, 84, 130
50.	B. nepalensis	1, 2	21
51.	B. nervosa	1	1, 21
52.	B. orientalis Shneid.	1	11
53.	B. orthobotrys	35, 37, 44, 58, 60, 64, 65	107, 108, 109
54.	B. ottawensis	1, 4, 14	76
55.	B. oblonga Shneid.	1, 2, 3, 4, 29, 35, 39, 44, 48, 49, 100, 106, 107, 108	84, 103, 104, 105, 106, 126, 130, 131
56.	B. pteolaris	1, 4, 44	33
57.	B. pseudoambalate	1, 4, 35, 36	89
58.	B. polymorpha	1, 2, 3, 6, 8, 22, 47, 107	111
59.	B. paucidentata Rusby.	1, 35, 36, 44, 45	44, 111
60.	B. regeliana	1, 44	76
61.	B. serrata Koehne.	1, 2, 3, 4, 6, 35, 44	31
62.	B. stolonifera	2, 29, 32, 37	112
63.	B. sibirica Pall.	1	11
64.	B. swaseyi	1, 44	21
65.	B. silvataroucana	1, 2, 4	21, 79
66.	B. thunbergii DC.	1, 2, 14, 44, 35, 45, 107	21, 89
67.	B. turcomanica Kar.	1	11
68.	B. trifoliata	1, 2	55
69.	B. tinctoria	1, 2, 4, 44	77
70.	B. tschonoskyana Reg.	2, 14, 35, 36, 46, 107	21
71.	B. umbelata	1	21
72.	B. valdiviana Phil.	24, 29, 33, 59, 60, 61, 66, 68, 69, 70, 71, 120, 125, 126	25, 119, 120, 121, 64, 123
73.	B. virescens Hook.	1, 3, 4, 6, 35, 44	118
74.	B. wilsonii	1, 2, 44, 45, 107	124
75.	B. vulgaris L.	1, 2, 3, 4, 6, 14, 18, 29, 35, 44, 45, 99, 107	76, 115, 116, 117
76.	B. zebiliana Shneider.	14, 44, 60	48, 125

Protoberberines

Protoberberines (PBs) are widely distributed alkaloids in the vegetable kingdom, and in barberries they form the bulk of the total alkaloids. In the plants, the alkaloids of this group are usually found in the form of protoberberine salts (Table 2, 1-8, 21-24), dihydroprotoberberines (18-20), tetrahydro derivatives (9-13, 21, 22), and 8-oxo derivatives (14-17, 25, 26). Plants of the *Berberis* genus have yielded 29 protoberberine alkaloids.

In the PBs isolated from barberries the substituents — hydroxy, methoxy, and methylenedioxy groups — are located at carbon atoms 2, 3, 9, 10, 11, 13, and 14. A hydroxy group is present at C-5 only in berberastine (24) [95]. Three alkaloids — dehydrocorydaline (7), corydaline (12), and thalictricavine (13) contain a methyl group at C-13.

Keto derivatives have been isolated mainly in recent years. They include O-methylprechileine (25), prepseudopalmatine (26), and 13-methoxy-8-oxoberberine (17). It is assumed that they are the products of the enzymatic oxidation in vivo of berberine (1), and palmatine (4) [25].

The structures of the protoberberine alkaloids, established with the use of modern spectral methods and classical organic chemistry, have been discussed in a series of reviews [34, 50] and monographs [18, 20].

In recent years, Pakistan species of barberry — *B. aristata* and *B. valdiviana* — have yieldeded the protoberberine alkaloids karachine (27) and valachine (28) [119], containing unusual bridge bonds. The maximum peak of the ion with m/z 336 in the mass spectra of these alkaloids has made it possible to assume that both alkaloids have a berberine skeleton. According to the PMR spectra, these two alkaloids differ from one another by one methyl group, while each has one methylenedioxy and two methoxy groups. It has been established with the aid of NOE that each of them has two bridge bonds: a $-CH_2-CH_2-$ group binds C-8 and 13, and a $-CH_2COCH_2-$ bridge binds C-14 and C-18. It has been established that karachine (27) is the product of the condensation of berberine with two molecules of acetone, while valachine (28) may be formed through the initial concentration of berberine with acetaldehyde followed by a second condensation with one molecule of acetone [119].

Bisbenzylisoquinoline Alkaloids

Plants of the genus *Berberis* have yielded 30 bisbenzylisoquinoiline (BBIQ) alkaloids. They are the most widespread among the dimeric isoquinoline alkaloids. At the present time, about 380 representatives are known. In the BBIQ alkaloids the two benzylisoquinoline residues may be linked by one, two, or three ether bonds, and they also include compounds with a carbon–carbon bond between the benzyl residues. In the barberries, BBIQ alkaloids with one and two ether bonds have been found.

Bisbenzylisoquinoline Alkaloids with one Diphenyl Ether Bond

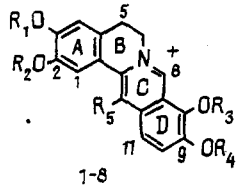
Of this subgroup, only six alkaloids have been found in barberries (Table 1). To establish their structures, the phenolic hydroxyls are usually methylated, and the resulting ether is oxidized with potassium permanganate or is cleaved with sodium in liquid ammonia. Then the structure of the alkaloid is established by studying the products obtained [110]. The UV spectra of alkaloids of this subgroup, like the spectra of other bisbenzyltetrahydroisoquinolines and tetrahydroisoquinolines exhibit a single maximum — in the 280-285 nm region — due to the presence of the tetrahydroisoquinoline nucleus. The UV spectra of the various subgroups of BBIQ alkaloids do not differ appreciably [132].

In the mass spectra of these alkaloids the molecular peak has a very low intensity. Its relative intensity is frequently less than 0.5 [26, 102, 123, 129]. The main peaks are those of ions formed as the result of two benzyl cleavages. The further fragmentation of these ions, formed from rings AB and A′B′, is insignificant. The mass of the main ion enables the presence and number of methoxy and hydroxy groups in the two isoquinoline parts of the molecule to be judged. If the compositions of the substituents in rings B and B′ are the same, as in the case of espinine 30 [129], a single intense ion peak appears in the spectrum.

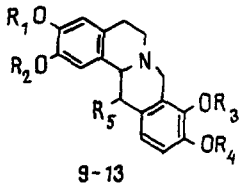
In PMR spectra of the alkaloids of this subgroup the features characteristic of benzyltetrahydroquinolines appear [88, 133]. Under the influence of the diamagnetic anisotropy of rings C and C′, methoxy groups at 7 and 7′ resonate in a strong-

TABLE 3. Classification and Structural Formulas of the *Berberis* Alkaloids

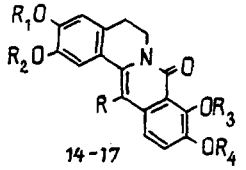
I. PROTOBERBERINES



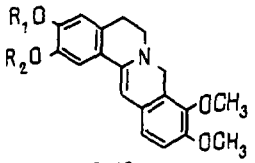
1-8



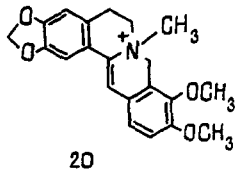
9-13



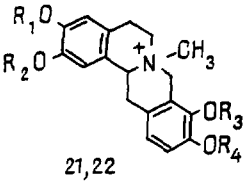
14-17



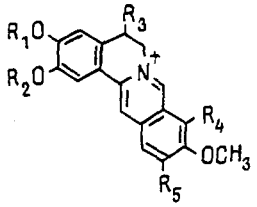
18,19



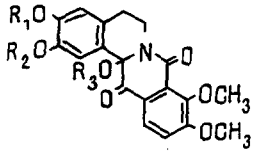
20



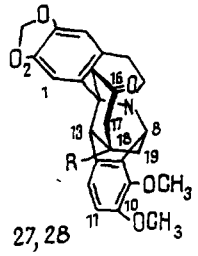
21,22



23,24



25,26

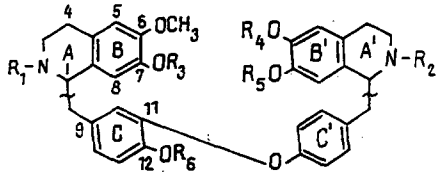


27,28

1. $R_1+R_2=CH_2;R_3=R_4=CH_3;R_5=H$
2. $R_1=R_5=H;R_2=R_3=R_4=CH_3$
3. $R_1=R_3=R_4=CH_3;R_2=R_5=H$
4. $R_1=R_2=R_3=R_4=CH_3;R_5=H$
5. $R_1=R_2=CH_3;R_3+R_4=CH_2;R_5=H$
6. $R_1+R_2=CH_2;R_5=R_3=H;R_4=CH_3$
7. $R_1=R_2=R_3=R_4=R_5=CH_3$
8. $R_1+R_2=CH_2;R_3=CH_3;R_4=R_5=H$
9. $R_1+R_2=CH_2;R_3=R_4=CH_3;R_5=H$
10. $R_1=R_2=R_3=R_4=CH_3;R_5=H$
11. $R_1+R_2=CH_2;R_3=R_5=H;R_4=CH_3$
12. $R_1=R_2=R_3=R_4=R_5=CH_3$
13. $R_1+R_2=CH_2;R_3=R_4=R_5=CH_3$
14. $R_1+R_2=CH_2;R_3=R_4=CH_3;R=H$
15. $R_1+R_2=CH_2;R_3=H;R_4=CH_3;R=H$
16. $R_1=R_2=R_3=R_4=CH_3;R=H$
17. $R_1+R_2=CH_2;R_3=R_4=CH_3;R=OCH_3$
18. $R_1+R_2=CH_2$
19. $R_1=R_2=CH_3$
21. $R_1=H;R_1=R_3=R_4=CH_3$
22. $R_1=R_3=CH_3;R_2=R_4=H$
23. $R_1+R_2=CH_3;R_5=OCH_3;R_3=R_4=H$
24. $R_1+R_2=CH_2;R_3=OH;R_4=OCH_3;R_5=H$
25. $R_1=R_2=CH_2;R_3=CH_3$
26. $R_1=R_2=CH_3;R_3=H$
27. $R=CH_3$
28. $R=H$

TABLE 3. (Continued)

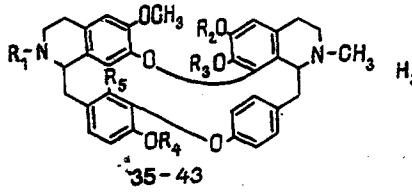
IIA. BISBENZOISOQUINOLINES WITH ONE DIPHENYL ETHER BOND



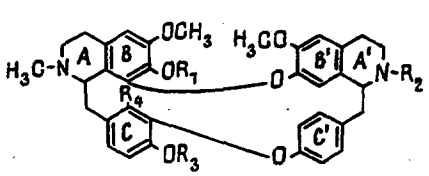
29 - 34

29. $R_1=R_2=R_4=CH_3;R_3=R_5=R_6=R_7=H$
30. $R_1=R_2=R_5=CH;R_3=R_4=R_6=R_7=H$
31. $R_1=R_2=R_5=R_6=CH_3;R_3=R_4=R_7=H$
32. $R_1=R_4=CH_3;R_2=R_3=R_5=R_6=R_7=H$
33. $R_1=R_2=R_3=R_4=CH_3;R_5=R_6=R_7=H$
34. $R_1=R_2=R_4=R_6=CH_3;R_3=R_5=H;R_7=OH$

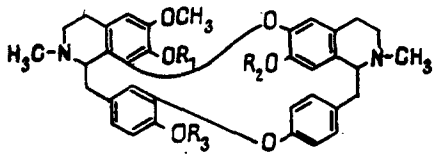
IIB. BISBENSOISOQUINOLINES WITH TWO DIPHENYL ETHER BONDS



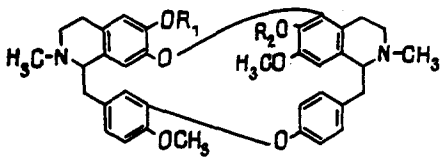
35 - 43



44-50



51,52

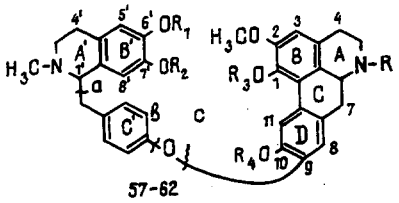


53-56

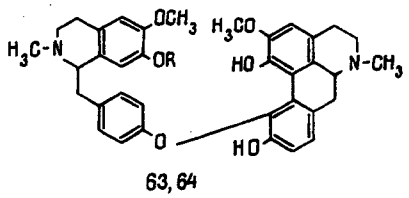
35. $R_1=R_2=R_3=CH_3;R_4=R_5=H$
36. $R_1=R_2=R_3=R_4=CH_3;R_5=H$
37. $R_1=R_2=CH_3;R_3=R_4=R_5=H$
38. $R_1=R_2=R_4=CH_3;R_3=R_5=H$
39. $R_1=(CH_3)_2;R_2=R_3=CH_3;R_4=R_5=H$
40. $R_1=R_2=R_3=CH_3;R_4=R_5=H$
41. $R_1=R_3=CH_3;R_2=R_4=R_5=H$
42. $R_1=R_2=R_4=CH_3;R_5=OCH_3;R_3=H$
43. $R_1=R_2=R_3=R_4=CH_3;R_5=OCH_3$
44. $R_1=R_2=CH_3;R_3=R_4=H$
45. $R_1=R_2=R_3=CH_3;R_4=H$
46. $R_2=CH_3;R_1=R_3=R_4=H$
47. $R_2=R_3=CH_3;R_1=R_4=H$
48. $R_1=CH_3;R_2=(CH_3)_2;R_4=R_6=H$
49. $R_1=R_3=CH_3;R_2=(CH_3)_2;R=H$
50. $R_1=R_2=R_3=CH_3;R_4=OCH_3$
51. $R_1=CH_3;R_2=H$
52. $R_1=R_2=H$
53. $R_1=R_2=R_3=CH_3$
54. $R_1=R_2=CH_3;\ R_3=H$
55. $R_2=CH_3;R_1=R_3=H$
56. $R_2=R_3=CH_3;R_1=H$

TABLE 3. (Continued)

III. APORPHINE-BENZYLISOQUINOLINE DIMERS



57-62

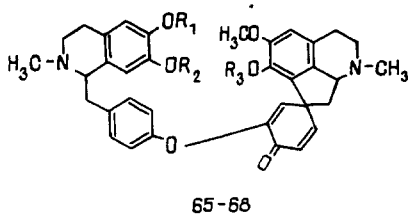


63, 64

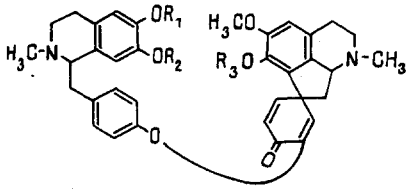
57. $R=R_1=R_2=CH_3;R_3=R_4=H$
58. $R_1=R_2=R_3=R=CH_3;R_4=H$
59. $R_1=R_2=CH_3;R_3=R_4=R=H$
60. $R_2=R_3=R_4=H;R=CH_3$
61. $R_3=R=CH_3;R_1=R_2=R_4=H$
62. $R_2=R=CH_3;R_1=R_3=R_4=H$

63. $R=H$
64. $R=CH_3$

IV. PROAPORPHINE-BENZYLISOQUINOLINE DIMERS



65-68

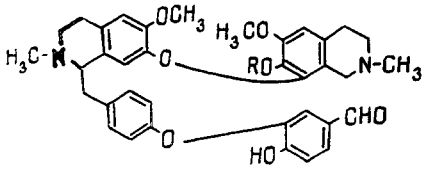


69-73

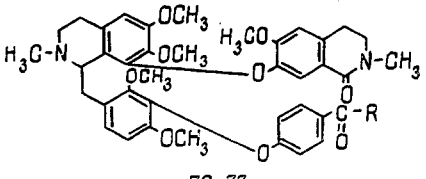
65. $R_1=R_2=R_3=CH_3$
66. $R_1=CH_3;R_2=R_3=H$
67. $R_2=CH_3;R_1=R_3=H$
68. $R_1=R_2=CH_3;R_3=H$

69. $R_2=CH_3;R_1=R_3=H$
70. $R_1=CH_3;R_2=R_3=H$
71. $R_1=R_3=CH_3;R_2=H$
72. $R_2=R_3=CH_3;R_1=H$
73. $R_1=R_2=CH_3;R_3=H$

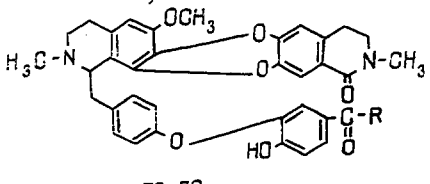
V. SECO-BISBENZYLISOQUINOLINE (SBBIQ) DIMERS



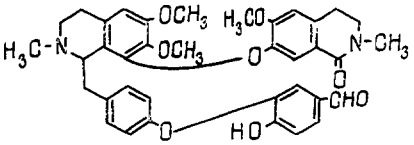
74, 75

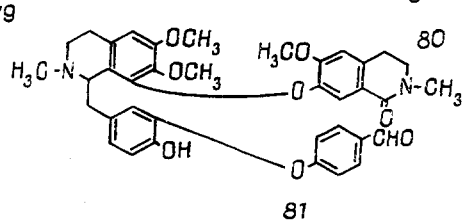


76, 77



78, 79





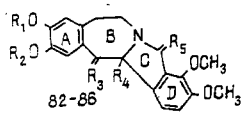
81

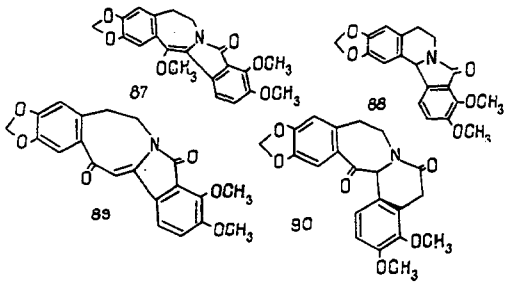
74. R=H
75. R=CH_3
76. R=H

77. R=OCH_3
78. R=H
79. R=OCH_3

TABLE 3. (Continued)

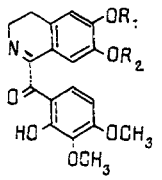
VI. ISOINDOLOBENZAZEPINES AND ALKALOIDS RELATED TO THEM

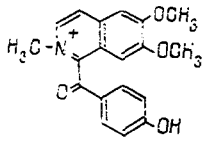


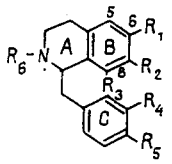


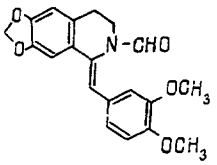
82. $R_1+R_2=CH_2;R_3=R_5=O;R_4=OH$
83. $R_1=R_2=CH_3;R_3=R_5=O;R_4=OH$
84. $R_1=R_2=CH_2;R_3=R_5=O;R_4=H$
85. $R_1=R_2=CH_2;R_3=H_2;R_4=H;$ $R_5=O$
86. $R_1+R_2=CH_2;R_3=R_5=H_2;R_4=H$

VII. BENZYLISOQUINOLINES

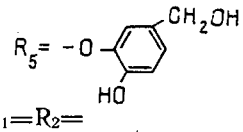








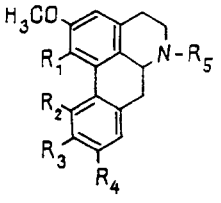
91. $R_1+R_2=CH_2;R_3=H_2$
92. $R_1=R_2=CH_3;R_3=O$
93. $R_1+R_2=CH_2$
94. $R_1=R_2=CH_3$
96. $R_1=R_2=R_4=R_5=OCH_3;R_6=$ $=CH_3;\ R_3=H$
97. $R_1=R_5=OCH_3;R_6=CH_3;R_4=$ $R_2=OH;R_3=H$
98. $R_1=OCH_3;R_2=R_5=OH;R_3=R_4=$ $=H;R_6=CH_3$
99. $R_2=OCH_3;R_1=R_4=H;R_3=R_5=$ $=OH;R_6=CH_3$
100. $R_2=OCH_3;R_1=R_4=H;R_3=R_5=$ $=OH;R_6=(CH_3)_2$
101. $R_1=OCH_3;R_2=OH;R_3=R_4=H;$ $R_6=CH_3$



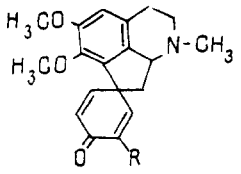
103. $R_3=R_4=H;R_5=OH;R_1=R_2=$ $=OCH_3;R_6=(CH_3)_2,N^+$

TABLE 3. (Continued)

VIII. APORPHINES AND PROAPORPHINES



104-112



113, 114

104. $R_1=R_3=R_4=OCH_3; R_5=CH_3; R_2=H$

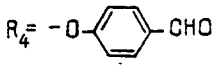
105. $R_1=R_4=OH; R_3=OCH_3; R_5=CH_3; R_2=H$

106. $R_1=OH; R_3=R_4=OCH_3; R_5=CH_3; R_2=H$

107. $R_1=R_2=OH; R_3=OCH_3; R_5=(CH_3)_2; R_4=H, N^+$

108. $R_1=R_3=OCH_3; R_2=OH; R_5=CH_3; R_4=H$

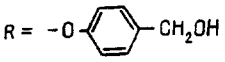
109. $R_1=R_3=OH; R_2=H; R_5=CH_3$



110. $R_1=R_3=OH; R_5=CH_3; R_1=R_4=H$

111. $R_1=R_2=R_3=OCH_3; R_4=H; R_5=(CH_3, O), N^+$

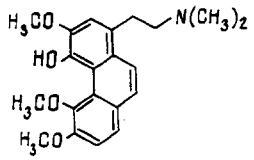
112. $R_1=R_2=H; R_3=OH; R_5=CH_3; R_4= -O-C_6H_4-CH_2OH$



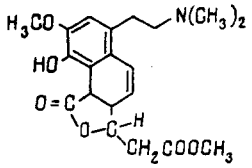
113.

114. R=H

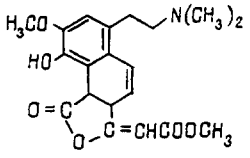
IX. CORYDINEMETHINE AND RELATED ALKALOIDS



115



116



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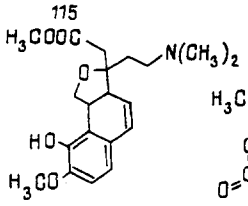

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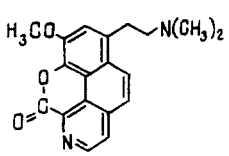
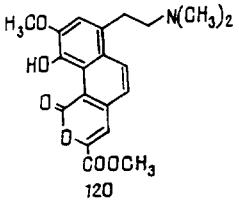
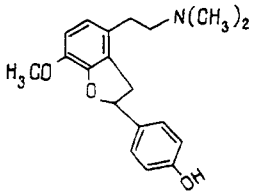


119

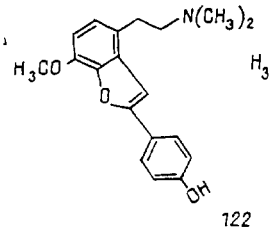


120

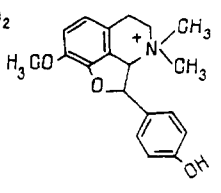
X. QUETTAMINE AND RELATED ALKALOIDS



121



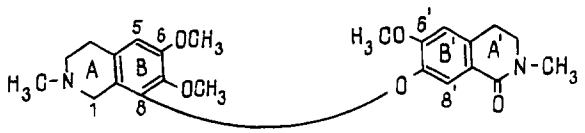
122



123

TABLE 3. (Continued)

XI. ISOQUINOLINE-ISOQUINOLONE DIMERS

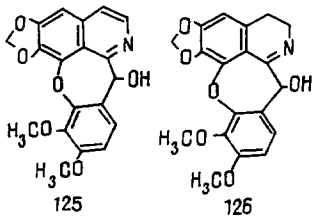


124

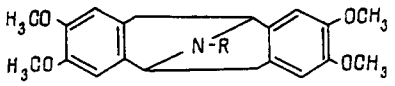
XII. CULARINE GROUP

XIII. PAVINE GROUP

127. R=H
128. R=CH_3



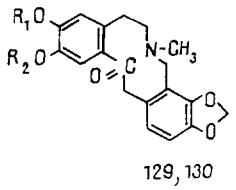
125 126



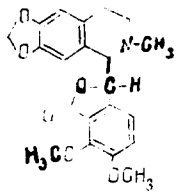
127, 128

XIV. PROTOPINE GROUP

XVI. PHTHALIDEISOQUINOLINES



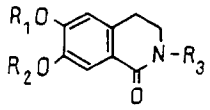
129, 130



131

129. R_1=R_2=CH_3
130. R_1+R_2=CH_2

XV. ISOQUINOLONES



132-134

132. R_1+R_2=CH_2; R_3=H
133. R_1=R_2=CH_3; R_3=H
134. R_1=OCH_3; R_2=H; R_3=CH_3

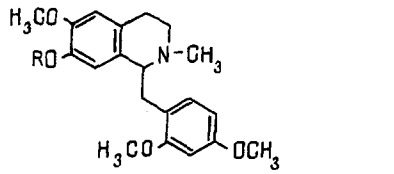
stronger field as compared with the signals of methoxy groups at C-6 and C-6′. The signals of a proton of a methoxy group at C-12 arre usually close to or coincide with the signals of methoxyls at C-6 and C-6′, while N-methyl groups give very close singlets in the 2.40-2.55 region or a six-proton singlet in the same region. Aromatic protons in positions 8 and 8′ are also present under the isotropic influence of rings C and C′ and resonate in a stronger field than the other aromatic protons.

Bisbenzylisoquinoline Alkaloids with Two Diphenyl Ether Bonds

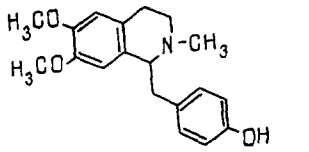
Barberries have yielded 22 bisbenzylisoquinoline alkaloids with two diphenyl ethyl bonds. The majority of them belong to the types of oxyacanthine (35-43) and berbamine (44-50), and the reminder to the types of thalmine (51, 52) and thalicberine (53-56).

Chemical and spectral methods for establishing the structures of these alkaloids have been discussed in detail in reviews [18, 61, 67, 88, 96, 102, 113, 114]. Two unusual representatives may be noted — calafatine (50) [46] and osornine (42) [26],

isolated from *B. buxifolia* and distinguished by an additional methoxy group in position 10. The cleavage of calafatine (50) with sodium in liquid ammonia gave the nonphenolic compound 50a, while O-methylosornine (43) (Table 3) gave compounds 50b and 50c.



50 a R=CH_3
50 b R=H



50 c

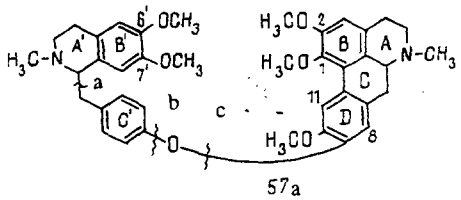
The structure of compound (50a) was established on the basis of its PMR spectrum. The number and nature of the substituents in rings A, B, A′, and B′ of these alkaloids were determined from the intensities of the ion with m/z 381 in osornine (42) and of the ions with m/z 396 and 485 in calafatine (50) while an ion with m/z 485 (M − 167) in calafatine (50) indicated the presence of two methoxyls in ring C, and therefore compound (50) was assigned to the alkaloids of the berbamine type, as was confirmed by the appearance of the signals of two N-methyl groups at 2.35 and 2.53 ppm. The signals of H-1 and H-1′ appeared at 4.21 and 3.72 ppm, respectively, and the signals of these protons in compound (42) were found at 3.65 and 4.20 ppm, respectively, which is apparently connected with the number of substituents and also with the position of the diphenyl ester bond in rings B and B′ [96].

In osornine (42) and O-methylosornine (43) the additional substituent in ring E causes a large upfield shift of the signal of the H-8 proton (4.59-4.80 ppm), while its influence on the 2-NCH_3 group is smaller, although its signal also shifts upfield (2.28 ppm) and differs from that of 2′-NCH_3 by 0.12 ppm. The signal of the H-8′ proton in calafatine (50) appears at 5.38 ppm [46]. Such an upfield shift is due to a disturbance of the conformation because of the presence of the substituent at C-10 [96].

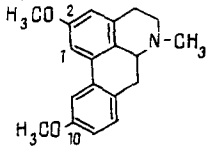
Aporphine-Isoquinoline Dimers

Alkaloids of this subgroup have been detected in plants of the genera *Berberis*, *Thalictrum* and *Hernandia*. Information on them has been given in reviews [64, 134]. Eighty representatives of them have been found in barberries and they are all coclaurine-aporphine dimers.

In establishing the structures of these alkaloids, they are usually, likewise, subjected to cleavage with sodium in liquid ammonia. Thus, from the cleavage of the 1,10-di-O-methyl ether of pakistanine (57a), (+)-armepavine (50c) and (−)-2,10-dimethoxyaporphine (57b) were isolated. In this process, the hydrogenolysis of the methoxy group at C-1 of the aporphine half took place [43]. At the present time, the structures of these alkaloids are established mainly by spectral methods, predominantly high-resolution ^1H NMR.



57a



57 b

In the UV spectra of the aporphine benzylisoquinolines (ABIQs), absorption maxima are observed in the 220-225, 265-270 (shoulder), 280 (shoulder), and 301-307 nm regions.

Each of the mass spectra contains the weak peak of the molecular ion, the maximum peak of an ion arising as the result of the benzyl cleavage "a", and the peaks of the $(M - a)^+$, $(M - b)^+$, and $(M - c)^+$ ions. The mass of ion "a" gives in-

formation on the nature of the substituents in rings A and B, while the ion of the $(M - c)^+$ type permits the number and nature of the substituents in the aporphine half of the molecule to be determined [43, 134].

In the PMR spectra of these alkaloids, the signals of the N-methyl groups (benzylisoquinoline and aporphine halves) almost coincide (2.50-2.52 ppm). Only in some of them does the signal of the N-methyl group of the aporphine half shift downfield by 0.1 ppm as compared with the signal of a N-methyl in the benzylisoquinoline moiety [64]. The signals of the methoxy groups at C-6′ and C-2 frequently coincide or give close chemical shifts, appearing in the 3.80-3.90 ppm. The signal of a methoxy at C-7′ appears in the 3.40-3.50 ppm region, which is connected with the screening influence of ring C′. The methoxy group at C-1 resonates in the 3.65-3.70 ppm region, which is characteristic for the aporphine alkaloids [135]. Aromatic protons at C-3 and C-5′ also give close signals — in the 6.50-6.60 ppm region. When a methoxy group is present at C-7′, the signal of the aromatic proton at C-8′ appears in a stronger field (5.85-5.90 ppm) while in the case where a hydroxyl is present in the same position the signal of this proton shifts downfield somewhat (6.16-6.37 ppm).

Proaporphine-Isoquinoline Dimers

The alkaloids of the proaporphine-benzylisoquinoline (PABIQ) group can be formed biogenetically on the intramolecular oxidative coupling of BBIQ alkaloids of the (+)-berbamunine type or alkaloids of similar structure [29]. Nine representatives of them have been found in barberries. On treatment with dilute mineral acids, they undergo a dienone-phenol rearrangement and are converted into ABIQs [43, 65]. In this way, pakistanamine (65) is converted into O-methylpakistanine (58), valdivianine (73) into pakistanine (57), berbivaldine (69) into porveniramine (62), and valdiberine (70) into chitraline (60). By means of this reaction it is possible to obtain valuable information on the structures of the PABIQ alkaloids. On the dienone-phenol transformation of these alkaloids, two series of ABIQ alkaloids may be formed; i.e., as the result of this reaction the rotation of ring D around the spiro center (C-13) may be dextrorotary or levorotary. In these circumstances, from alkaloids (65), (69), (70), (71), (72), and (73), which include the "normal" stereochemistry at the C-spiro center, ABIQs are formed with substitution at C-1, -2, -9, and -10 in the aporphine half, and, correspondingly, from alkaloids (66), (67), and (68) (epi-series) the dienone-phenol rearrangement gives C-1, -2, -10, and -11-substituted ABIQs [49].

The stereochemistry of the C-13 spiro center has been studied for alkaloids of the pakistanamine (65), rupancamine (75), and epiberbivaldine (67) type [49]. It has been established by a study of the PMR spectra and also by measuring intramolecular NOEs that a sterically hindered situation is created around the C-13 spiro center of these alkaloids. The steric constriction around this center depends on the configuration of the 6a-H atom. When it has the R-configuration, during the process of dienone-phenol rearrangement the dienone system undergoes levorotatary transformation, and when it has the S-configuration dextrorotary transformation. Thus, the steric constriction around the C-13 spiro center is the main factor acting on the process of dienone-phenol transformation [49].

The UV spectra of the PABIQ alkaloids are characterized by absorption maxima in the 210-225, 230 (shoulder), and 280-285 nm regions. The mass spectra show weak peaks of the molecular ions M^+ and the maximum peaks of the ions formed on cleavage "a." In addition, there are the ions arising on cleavages "b" and "c" (Table 3). The characteristic cleavages on the mass fragmentation of these alkaloids are similar to those of the aporphine-benzylisoquinolines [43, 134].

The PMR spectra of the PABIQ alkaloids are close to those of the ABIQ alkaloids, with the exception of the signal of the N-methyl group of the proaporphine moiety, which appears in a weaker field (2.50-2.55 ppm), differing considerably (by 0.15-0.18 ppm) from the signal of the N-methyl group in the benzylisoquinoline half [29].

Secobisbenzylisoquinoline Alkaloids

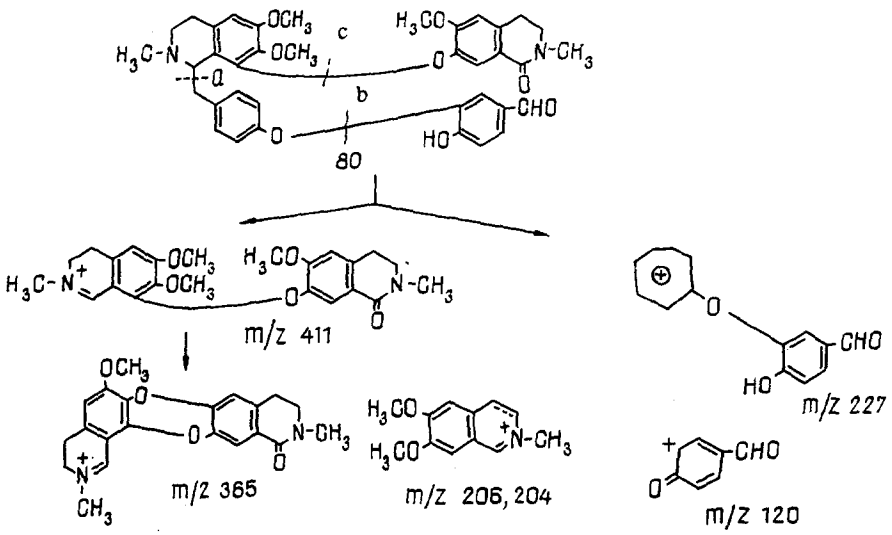
The first representative of the secobisbenzylisoquinoline (SBBIQ) alkaloids was baluchistanamine (80), which was isolated in 1974 from *B. baluchistanica* [42]. At the present time, eight alkaloids of this type have been isolated from various *Berberis* species: jhelumine (74), chenabine (75) [25], curacautine (76), thalcamine (77), punjabine (78), gilgitine (79), baluchistanamine (80), and sindamine (81). They may be considered as the products of the *in vivo* oxidation of the BBIQ alkaloids or of the condensation of alkaloids of the type of karakoramine (101) with simple isoquinoline alkaloids. Thus, they may be united under the name of isoquinoline-benzylisoquinoline and isoquinolone-benzylisoqinoline dimers.

In the UV spectra of jhelumine and chenabine, absorption maxima are observed in the 210, 227 (shoulder), 281, and 326 nm regions, and in the others, which have amide carbonyls, absorption maxima in the 207-210, 220-230, 260-280, and 305 nm regions. Furthermore, in the spectrum of punjabine (78) and that of gilgitine (79) there is an additional band in the 325 nm region.

The IR spectra of these alkaloids contain absorption bands of amide carbonyls (1605-1610 and 1640-1645 cm^{-1}) and of conjugated aldehyde carbonyls (1690-1720 cm^{-1}).

Important results in the establishment of the structures of these alkaloids have been obtained by mass-spectrometric analysis. This may be illustrated by the case of baluchistamine (80) (Scheme 1) [42]. In its mass spectrum there are the weak peaks of the molecular ion M^+ with m/z 638 ($C_{37}H_{38}N_2O_8$), the maximum peak of an ion with m/z 411 ($C_{23}H_{27}N_2O_5$), and other informative peaks of peaks of ions with m/z 365 ($C_{21}H_{21}N_2O_4$), 227 ($C_{14}H_{11}O_3$), 206 ($C_{12}H_{16}NO_2$), 204 ($C_{12}H_{14}NO_2$) and 120 ($C_7H_4O_2$). The most important of them are the ions with m/z 411 and 227, which give an idea of the molecule. From the mass of these ions it is possible to judge the number and nature of the substituents in the isoquinoline and benzyl moieties of the alkaloid molecule.

Scheme 1



In the ^1H NMR spectra of jhelumine (74) and chenabine (75), the signals of the N-methyl groups appear very close to one another in the 2.50-2.55 ppm region. In chenabine (75), the protons of the methoxy groups at C-7 in ring B′ resonate in a fairly strong field of the spectrum at 3.25 ppm. The signal of the proton at C-8 in ring B is also shifted sharply upfield and is seen in the 5.23-5.33 ppm region [95]. This can be explained by the shielding influence of ring B′ in accordnce with the position of the diphenyl ether bond between C-7 and C-8′.

In the ^1H NMR spectra of the alkaloids curacautine (76), thalcamine (77), baluchistamine (80) and sindamine (81), the signal of the N-methyl group of the isoquinoline moiety appears at 3.04-3.10 ppm, i.e., it is shifted downfield by 0.75-0.84 ppm relative to the signal of the N-methyl group of the benzylisoquinoline moiety. In the alkaloids punjabine (78) and gilgitine (79), the signal of the N-methyl group in the isoquinoline moiety appears at 3.17 ppm. Under the influence of the carbonyl of the aldehyde group in each of alkaloids 76-81, the signal of the aromatic protons of ring C′ resonate in a weaker field than the other aromatic protons. The amide carbonyl in the same alkaloid shifts the signal of the aromatic proton at C-8′ into the 7.16-7.29 ppm region.

Isoindolobenzazepines and Alkaloids of Similar Structure

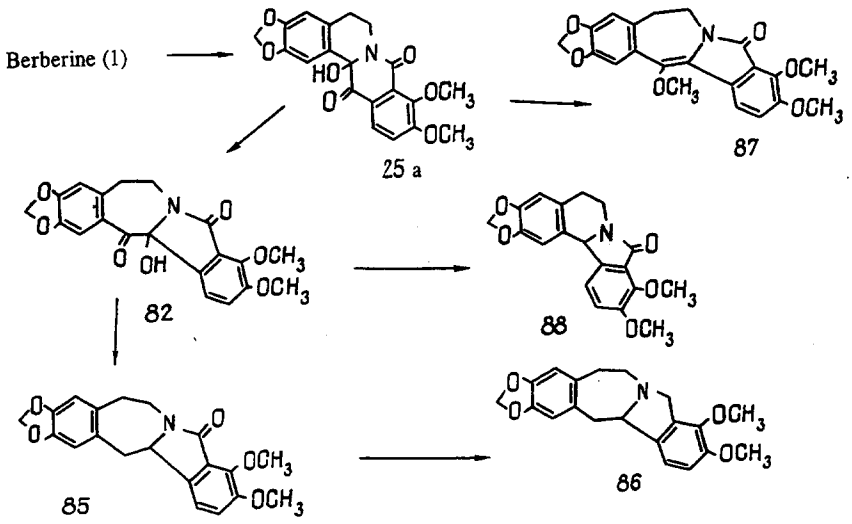
Nine alkaloids belonging to this subgroup have been isolated from plants of the *Berberis* genus. Of them, alkaloids 82-87 are isoindolobenzazepines, while nuevamine (88) belongs to the isoindoloisoquinolines, magellanesine to the isoindoloben-

zazocines, and puntarenine (90) to the isoquinolinobenzazepines (Table 3). Chileninone, isolated from *B. actinicantha* [25], was later shown to be identical with berberrubine (6) [136]. Puntarenine, isolated from *B. empetrifolia* [68] is apparently identical with the isohomoprotoberberine alkaloid isolated from *B. actinicantha* [22], materials on the proof of the structure of which were published almost simultaneously.

In the opinion of Valencia et al. [25], the detection of a number of isoindolobenzazepine alkaloids in barberries together with oxidized protoberberine alkaloids such as 13-methoxy-8-oxoberberine (17), O-methylprechilenine (25), 8-oxopalmatine (16), and prepseudopalmanine (26) to some degree explain the biogenesis of these alkaloids. The initial enzymatic oxidation of berberine (1) in the plant possibly leads to 13-hydroxy-8-oxoberberine (17a), which has not yet been isolated from plants. The latter, on *in vivo* methylation, forms 13-methoxy-8-oxoberberine or is converted into (25a). In acidified methanol, O-methylprechilenine (25) is formed from it. The isomerization of (25a) in the plant may also form chilenine (82). It is most likely that 13-deoxychilenine (84) is formed from chilenine (82) by dehydration followed by reduction [25]. It could be assumed that pictonamine (87) is an artefact obtained from (84). However, it has been shown experimentally that, in ethanolic solution, compound (87) is not formed from (84) in 48 h [25].

The transformation of the protoberberine alkaloids into isoindolobenzazenines and the interconversions of the latter have been achieved under laboratory conditions.

Scheme 2

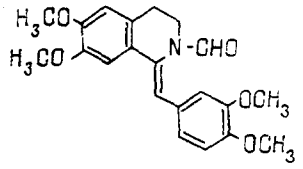


Thus, chilenine (82) has previously been synthesized from prechilenine (25a), which, in its turn, was obtained by the oxidation of berberine (1) [137], while lennoxamine (85) was obtained from (82) by reduction with zinc in hydrochloric acid [138]. The reduction of (85) with B_2H_6 gave chilenamine (86) [139], which had been synthesized previously by Schopf [140]. The alkaloid pictonamine (87) has also been obtained in several stages from chilenine (Scheme 2) [138].

Thus, the isoindolobenzapenines and alkaloids structurally close to them can be considered as new type of alkaloids within the isoquinoline group the precursors of which are the protoberberines.

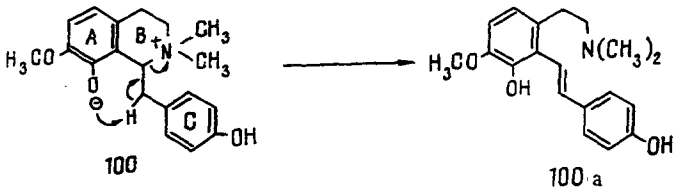
Benzylisoquinoline Alkaloids

Plants of the *Berberis* genus have yielded 13 benzylisoquinoline alkaloids (91-103), and four of them — berbitine (91), taxilamine (92), dihydrorugosine (93), and dihydrotaxilamine (94) — having hydroxy and methoxy substituents in positions C-10, C-11, and C-12 of ring C — belong to the subgroup of pseudobenzoisoquinoline alkaloids. Although they form a small group they hae already been detected in plants of the Anonaceae, Berberidaceae, Ranunculacaeae, and Fumaracaeae families. They are possibly formed as the result of the oxidation of protoberberine salts, via alkaloids of the type of polycarpine (102a) and polyberberine (102) [149].



102a

The oxygen substituents in the overwhelming majority of the benzoisoquinolines formed from the usual biogenetic precursors are pressent in positions 6 and 7. Only juzifine (99) and oblongine (100) belong structurally to the unusual 7,8-substituted benzylisoquinolines. Another exception is formed by the cularine group having, as is assumed, a 7,8-substituted benzoisoquinoline precursor [147]. It has been reported that oblongine (100), isolated in the form of the iodide, undergoes the Hofmann degradation under exceptionally mild conditions forming the des- base (100a) [148]. The presence of an ion with m/z 313 in the mass spectrum of (100) indicates that this degradation takes place even under the conditions of mass spectrometry. This can be explained by the influence of the hydroxy group at C-8 on the β-hydrogen atom with respect to the quaternary nitrogen.



100 100a

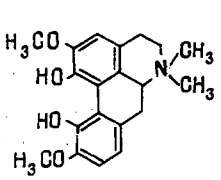
A characteristic feature of the PMR spectrum of (100) is the downfield shift of the signal of the proton at C-1 (5.38 ppm (1 H, q)). This indicates that it is under the influence not only of the quaternary nitrogen atom but also of the hydroxyl at C-8. A pronounced downfield shift of the C-1−H proton is observed in the PMR spectrum of the tertiary alkaloid juzifine (99) — a quartet at 4.13 ppm [146].

Group of Aporphine and Proaporphine Alkaloids

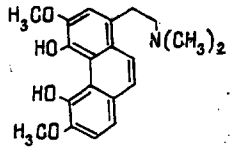
Alkaloids of the aporphine group are widespread among the isoquinoline alkaloids. More than 500 representatives of them have been isolated from more than 80 plant genera belonging to 20 families of the Earth's flora [135, 141, 142, 144, 145]. Among the barberry species studied, alkaloids of the aporphine group are encountered fairly rarely, with the exception of magnoflorine (107), which has been isolated from 16 *Berberis* species (Table 2). Before the isolation of glaucine (194) from *B. julianae* [86], magnoflorine remained the only representative of the aporphines among *Berberis* alkaloids. At the present time, 12 aporphine alkaloids have been isolated from plants of the *Berberis* genus. Only two representatives of the proaporphine alkaloids have been isolated from barberries: coyhaiquine (113) and pronuciferine (114). The isolation of benzylisoquinoline, aporphine, and proaporphine alkaloids from a barberry satisfactorily explains the formation of aporphine-benzoisoquinoline and proaporphine-benzoisoquinoline akaloids in it.

Corydinemethine and Related Alkaloids

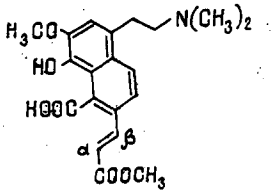
On the basis of the closeness of some of their structural elements, corydinemethine (115), chiloenamine (116), chiloenine (117), aconcaguine (118), santiagonamine (117), and andesine (120) have been assigned to the alkaloids of this subgroup. It may be assumed that the biogenetic precursor of these alkaloids is magnoflorine (107) which makes up a considerable part of the total quaternary alkaloids in plants of the *Berberis* genus.



107



107 a



107 b

On the intradiol breakdown of ring C in magnoflorinemethine (107a), derivative (107b) is formed, which may then cyclize in either of two directions. The cyclization of (107b) at C$-\alpha$ leads to andezine (120). On the other hand, cyclization at C$-\beta$ forms chiloenamine (110), which may then be oxidized to chiloenine (117). Aconcaguine may be regarded as the product of the intradiol cleavage of ring A in magnoflorinemethine (107a) [27].

The main peak in the mass spectrum of each of these alkaloids is that of an ion with m/z 58, representing the imminium cation $CH_2N-(CH_3)_2$, while the molecular ion is weak. Characteristic for the ^1H NMR of alkaloids (116-120) is the presence of two one-proton doublets in the 7.06-8.08 region with J = 8.5 Hz, relating to the two ortho-located aromatic protons of ring B, while in the spectrum of (120) these doublet signals are close and appear at 7.48 and 7.59 ppm.

Quettamine and Related Alkaloids

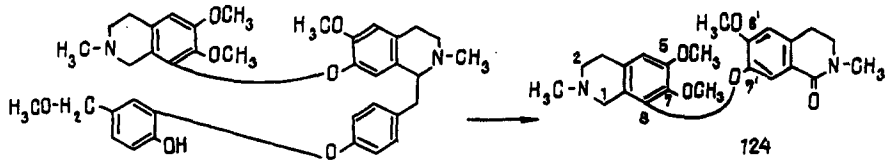
These alkaloids include benzofuran or dihydrobenzofuran rings in their structures. They include quettamine (123), dihydrosecoquettamine (121), and secoquettamine (122), which have been isolated from *Berberis baluchistanica* [39]. The Hofmann degradation of (123) forms secoquettamine (122), and Emde reduction yields dihydrosecoquettamine (121) and the stilbene des-base (100a).

In the mass spectra of three alkaloids, the peaks of ions with m/z 58 formed by the splitting out of the $[CH_2-N(CH_3)_2]^+$ fragment are intense, while the peaks of other ions, including M^+, have a low intensity. A characteristic feature of the NMR spectra of (123) is the presence of two doublets, at 5.47 and 5.94 ppm, with J = 9.8 Hz which are assigned to the protons at C-1 and C-9, respectively. The presence of two one-proton quartets with centers at 2.97 and 3.96 ppm and a triplet at 5.64 ppm from an ABX system indicates the presence of a dihydrobenzofuran ring in dihydroquettamine. A one-proton singlet at 7.07 ppm in the NMR spectrum of secoquettamine is assigned to a furanyl proton in a benzofuran ring.

In the opinion of Shamma et al. [39], a possible biogenetic precursor of quettamine (123), and alkaloids related to it is oblongine (100), from which a dihydrofuran system can be formed by *in vivo* oxidation at C$-\alpha$ followed by attack of the phenolic hydroxyl at C-8.

Isoquinoline-Isoquinolone Dimer Group

The first representative of alkaloids of this group was berbidine (124), isolated from *Berberis brandisiana* Ahrendt, growing in the mountains of northern Pakistan [150]. The IR spectrum of berbidine has absorption bands at 1605 and 1640 cm^{-1} . Its mass spectrum shows a molecular ion with m/z 412 (51%) and the maximum peak of an ion with m/z 411 (M — 1). Other fragments worthy of attention are shown by the peaks of ions with m/z 221, 206, and 190, formed as the result of the breakdown of the dimer on each side of the diaryl ether bond. In the PMR spectrum of berbidine signals have been detected from two N-methyl groups at 2.47 and 3.06 ppm, and from three methoxy groups at 3.82, 3.99, and 3.65 ppm. The latter have been ascribed to a C7-methoxyl on the basis of a comparison with the spectra of related BBIQ alkaloids [96]. In the aromatic region of the spectrum there are three well-resolved one-proton singlets, one of which, present in the weak-field region at 7.22 ppm, represents the H-8′ proton in the peri-position with respect to the oxygen of an amide carbonyl. On the basis of the spectral characteristics given, structure (124) has been proposed for berbidine. To confirm this structure, the methyl ether of chenabinol (124a) has been converted into berbidine by oxidation with $KMnO_4$ [150].



124 a

124

In addition to the groups of alkaloids considered above, representatives of other groups have been isolated from barberries: the new cularane alkaloids (125) and (126) [120], the pavine alkaloids (127) and (128) [47], the protopine alkaloids (129) and (130) [71, 98], the isoquinolones (132), (133), (134) [43, 44], and the phthalideisoquinoline alkaloid d-β-hydrastine (131) [31].

Thus, at the present time, about 80 species of plants of the genus *Berberis* growing in various regions of the terrestrial globe have been studied and about 140 bases have been isolated. They belong to 16 groups of isoquinoline alkaloids. Of them, the isoindolobenzazidines, the secobisbenzylisoquinolines, quettamine, and berbidine belong to new types of isoquinoline alkaloids.

Biological Activity of the *Berberis* Alkaloids

In consideration of the *Berberis* alkaloids from the point of view of biological activity, the most promising are the protoberberine alkaloids. Among them, berberine, which is the main alkaloid of this genus, is being used in medicine at this time as a cholagogue, while a tincture from the leaves of *B. amurensis* and an aqueous tincture of the leaves of *B. vulgaris* have been approved for use as agents for the treatment of metrorrhagias linked with inflammatory processes [9].

Berberine is used in chronic hepatitis, hepatocholecystitis, gallstone diseases and cholecystitises. Investigations showing a cytostatic, antibacterial, and heparin-antagonistic action of berberine sulfate and chloride [62, 152-154, 160] deserve attention. In recent years, Ukrainian scientists have recommended a number of promising cytostatic drugs based on berberine [12]. It has been established that berberine possesses an inhibitory activity against the growth of blood cancer cells [34]. (±)-Tetrahydroberberine exerts a pronounced sedative-tranquillizing action [155]. Palmitine exerts a stimulant action in the region of the peripheral cholinoreactive systems, raising the sensitivity of the rectus abdominis muscle to acetylcholine, and exerts a tonic effect on the smooth musculature of the intestine [152]. Palmitine chloride is used for the prophylaxis and tareatment of eye diseases, especially infectious diseases. Positive results have been obtained in the treatment of trachoma [153].

The alkaloids oxyacanthine and berbamine possess a hypotensive action, and their methiodides a pronounced curaremimetic action [158]. Oxyacanthine dihydrochloride exerts an action on yeast fungi, where it is stronger than antibiotics, and in the form of a 5% paste in lanoline is used in cases of deep caries, and acute partial and total pulpitises [158]. Of the aporphine alkaloids, magnoflorine possesses a hypotensive action [152], and thalicmidine central adrenolytic and antitussive actions [143].

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