DITERPENOIDS OF THE CLERODANE SERIES

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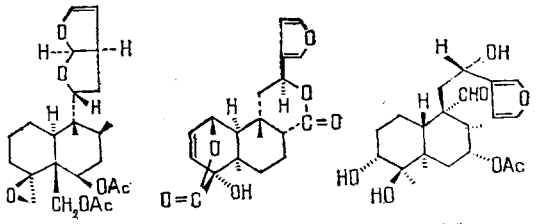
The review considers advances in the field of the study of natural clerodane diterpenoids, with coverage of the literature up to February, 1985.

GENERAL INFORMATION

In the chemistry of natural compounds in the last 10-15 years, a new group of natural bicyclic diterpenoids — diterpenoids of the clerodane series — has stood out quite distinctly. The accumulation of a large amount of factual material on substances of this kind and the absence of reviews (Hanson's brief communications [1-8] have a purely descriptive nature) have led to the necessity for generalizations and systematization of the compounds isolated.

Individual diterpenoids of the clerodane series such as clerodin (I) [9-13], columbin (II) [14-16], and cascarillin (III) [17] were known long ago, and their structures were established in the 60s mainly as the result of the development of investigation and, in particular, the possibility of performing X-ray structural analysis.

The clerodane diterpenoids belong to the group of diterpenoids with a rearranged labdane skeleton (ent-labdane). Sometimes substances of this type are called diterpenoids of the cascarillin group, ent-clerodanes, neo-clerodanes, and clerodanes. The name clerodanes is derived from clerodin (I) — the bitter principle from *Clerodendron infortunatum*, the structure of which was established in 1961 on the basis of an x-ray structural analysis of its bromolactone and was confirmed chemically and spectrally by the investigations of Barton and his colleagues [9-13].



I II III

The clerodane diterpenoids belong to the bicyclic terpenoids derived from decalin which form naphthalene derivatives on dehydrogenation [17]. The carbon skeleton of the clerodane diterpenoids differs from the labdane skeleton by the position of the methyl groups. J. W. ApSimon [22] showed that the clerodane skeleton is derived biosynthetically from the labdane skeleton through a rearrangement of the basic skeleton accompanied by hydride and methyl shifts [22].

The carbon skeleton of the clerodane diterpenoids does not correspond to Ruzicka's isoprenoid rule [23]. In view of what has been said above, it is necessary to dwell on possible systems of numbering the carbon atoms for clerodane diterpenoids. The generally adopted system of numbering is closest to the numbering proposed by Cocker and Halsall (IV) [17, 21, 24, 25].

Another system of numbering is universally used which reflect the biogenetic relationship between the bicyclic and tricyclic diterpenoids (V) [26]. Cases are known of an arbitrary numbering of the side chain [27].

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TABLE 1. Natural Clerodane Diterpenoids

	Compound	Composition	mp, °C	$[\alpha]_D$, deg	Source of isolation	Literature
			I. Teucrin group			
1.	Teucrin	$C_{19}H_{20}O_5$	207-208	+88.4 (chl)	*Teucrium viscidum*	35
2.	Teucrin A	$C_{19}H_{20}O_6$	251-253	+190 (chl)	*Teucrium chamaedrys*	29
3.	Teucrin B	$C_{20}H_{24}O_7$	239-241	+5.5	"	30
4.	Teucrin E	$C_{20}H_{24}O_6$	235-238	+25	"	30
5.	Teucrin F	$C_{20}H_{22}O_7$	225-230	+6.0 (pyridine)	"	30
6.	Teucrin G	$C_{20}H_{22}O_8$	245-249		"	30
7.	Teucvidin	$C_{19}H_{20}O_5$	214	−70.0 (chl)	*Teucrium viscidum var. miguelianum*	31
8.	Teucrin P	$C_{20}H_{24}O_5$	Oil	+21.4 (chl)	*Teucrium polium*	32
9.	Picropolin	$C_{22}H_{26}O_8$	199-201	+44.5 (chl)	"	36
10.	Montanin E	$C_{20}H_{28}O_7$	219-223	23.5 (acetone)	*Teucrium montanum*	37
11.	Montanin F (teucjaponin)	$C_{22}H_{28}O_7$	143-146	+46	"	37
12.	Capitatin	$C_{24}H_{28}O_9$	165	−166	*Teucrium capitatum*	37
13.	Teupolin IV	$C_{22}H_{26}O_8$	196-198	+90.9	*Teucrium polium*	39
14.	Teupolin V	$C_{20}H_{26}O_6$	194-197	−24.4 (acetone)	"	39
15.	Salvifarin	$C_{20}H_{20}O_6$	220-222	−53.9 (chl)	*Salvia farinaceae*	40
16.	Salvifaricin	$C_{20}H_{18}O_5$	214-215	−155.2	"	40
17.	Teuscordinone	$C_{20}H_{20}O_6$	235	−84.1 (dioxane)	*Teucrium scordium*	41
18.	Teucrin H_1	$C_{19}H_{20}O_6$	181-182	−95 (chl)	*Teucrium girganicum*	42
19.	Teucrin H_2	$C_{20}H_{24}O_6$	212-214	−12 ± 4 (chl)	"	42
20.	Teucrin H_3	$C_{22}H_{26}O_7$	216-218	+89 ± 4 (chl)	"	42
21.	Teucrin H_4	$C_{19}H_{20}O_6$	225-226	+48 ± 4 (chl)	"	42
22.	Teupyrenone	$C_{22}H_{26}O_7$	213-215	−46.5 (chl)	*Teucrium pyrenaicum*	43
23.	Teupyreinin	$C_{26}H_{32}O_{10}$	112-114	−9.4 (chl)		43
24.	Teupyreinidin	$C_{28}H_{36}O_{11}$	102-108	+26.7		43
25.	Gnaphalin	$C_{20}H_{24}O_6$	172-174	−46.6 (chl)	*Teucrium gnaphalodes. L. Her.*	44
26.	Gnaphalidin	$C_{24}H_{30}O_8$	132	−36.5	"	44
27.	Acetylgnaphalin	$C_{22}H_{26}O_7$	227-229	+82	"	44
28.	Crotocaudin	$C_{19}H_{18}O_5$	199-200 (decomp.)	−65	*Croton caudatus*	33
29.	20-Deacetylerio-cephalin	$C_{22}H_{28}O_8$	Amorph. 104-111	+118.9	*Teucrium lanigerum*	45
30.	Isoeriocephalin	$C_{24}H_{30}O_9$	232-234	−33.1	*Teucrium lanigerum*	45
31.	Eriocephalin	$C_{24}H_{30}O_9$	197-200	+76.1	*Teucrium eriocaphalum*	46
32.	Teuflidin	$C_{19}H_{20}O_6$	178	100	*Teucrium flavum*	47
33.	Teumarin	$C_{22}H_{28}O_8$	Amorph. 98-107	+34.1	*Teucrium marum*	49
34.	Montanin C	$C_{24}H_{30}O_8$	184-186	+8.4	*Teucrium flavum ssp. glaucum*	50
35.	Teupolin I	$C_{22}H_{28}O_7$	211-213	+60	"	50
36.	12-Epiteucvin	$C_{19}H_{20}O_5$	197-199	+222.6	"	50
37.	Ketone		218-219	+44.4	*Teucrium polium*	51
38.	Corylifuran	$C_{22}H_{26}O_8$	181-184	+44	*Croton corilifolius Lam.*	52
			II. Elongatolide group			
39.	Elongatolide A	$C_{20}H_{30}O_3$	Oil		*Solidago elongata Nutt*	53
40.	Elongatolide B	$C_{22}H_{32}O_4$	Oil		"	53
41.	Elongatolide C	$C_{25}H_{36}O_4$	Oil		"	53
42.	Elongatolide D	$C_{22}H_{32}O_5$	Oil		"	53
43.	Elongatolide E	$C_{25}H_{36}O_5$	Oil		"	53
44.	Component G	$C_{20}H_{30}O_3$	Oil	−21	*Solidago serotina*	54

TABLE 1 (Continued)

	Compound	Composition	mp, °C	$[\alpha]_D$, deg	Source of isolation	Literature
45.	Component I		Oil	−9	*Solidago serotina*	54
46.	Marrubiaside	$C_{26}H_{38}O_9$	149-150		*Leonurus marrubiastrum*	55
47.	Marrubialactone	$C_{20}H_{26}O_5$	212-213		"	55
48.	Deoxymarrubialactone	$C_{20}H_{26}O_4$	189-191	−28.3	*Chaiturus marrubiastrum*	56
49.	Ajugarin I	$C_{24}H_{34}O_7$	155-157		*Ajuga remota*	57
50.	Ajugarin II	$C_{22}H_{32}O_6$	188-189		"	57
51.	Ajugarin III	$C_{24}H_{36}O_8$	243-245		"	57
52.	Methyl 16-oxo-15,16-dehydrohardwickiate	$C_{21}H_{30}O_4$	Oil		*Printzia laxa*	20
53.	Marrubiastrol	$C_{20}H_{26}O_5$	179-180	−70	*Leonurus marrubiastrum L.*	58
54.	Aldehydomarrubialactone	$C_{20}H_{24}O_5$	176-178	−31.4	"	58
55.	Methyl 15-hydroxy-16-oxo-15,16-dihydrohautriwate		Oil	−73	*Conyza scabrida*	21
56.	Gutierolide	$C_{21}H_{31}O_5Cl$	207-209	−103 (methanol)	*Gutierrezla dracunculoides*	59
57.	Ajugamarin	$C_{29}H_{40}O_{10}$	93-95		*Ajuga nipponensis*	60
58.	Dilactone I	$C_{20}H_{26}O_4$	150		*Simphiopappus italiensis*	61
59.	Dilactone II	$C_{20}H_{28}O_5$	229-230		"	61
60.	Diterpenoid 1	$C_{20}H_{28}O_4$	151-153		*Baccharis trimera*	62
61.	Diterpenoid 2	$C_{20}H_{26}O_5$	203-205		"	62
62.	Diterpenoid 3	$C_{20}H_{26}O_5$	195-196	−97	"	62
			III. Columbin group			
63.	Columbin	$C_{20}H_{22}O_6$	194	−67 (pyridine)	*Jatorrhiza palmata Miers.*	14, 15,16
64.	Chasmanthin	$C_{20}H_{22}O_7$	225-228	0 (pyridine)	"	63, 64
65.	Palmarin	$C_{20}H_{22}O_7$	253-258	+17 (pyridine)	"	63, 64
66.	Jateorin	$C_{20}H_{22}O_7$	Oil		"	63, 64
67.	Cascarillin A	$C_{20}H_{28}O_5$	187-203	−61	*Croton eleuteria*	17
68.	Tinophyllone	$C_{21}H_{24}O_6$	175	−98	*Tinomiscium philippiense*	65
69.	Fibleucin	$C_{20}H_{20}O_6$	169-172	−28 (pyridine)	*Fibraurea chloroleuca*	66
70.	Fibraurin	$C_{20}H_{20}O_7$	288-289	−28 (c 1.04; pyridine)	"	67
71.	6-Hydroxyfibraurin	$C_{20}H_{20}O_8$	303-304	+23.6 (c 1.13; pyridine)	"	67
72.	Floribundic acid	$C_{20}H_{23}O_5$	250	−130	*Evodia floribunda Baker.*	68
73.	Methyl barboscoate	$C_{21}H_{26}O_5$	152-153	−76	*Croton californicus*	28
74.	Bacchotricuneatin A	$C_{20}H_{22}O_4$	239-241	−121.4	*Baccharis truncuneata*	69
75.	Bacchotricuneatin B	$C_{20}H_{22}O_5$	191-192	−93.3 (chl)	"	69
76.	Bacchotricuneatin C	$C_{20}H_{22}O_5$	188-190			69
77.	Salviarin	$C_{20}H_{22}O_5$	218	−85	*Salvia splendens*	70
78.	Isojate	$C_{20}H_{22}O_7$	165-167	+30 (pyridine)	*Jatorrihiza palmata Miers.*	63, 64

TABLE 1 (Continued)

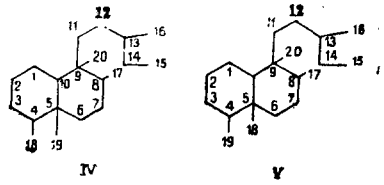
Compound	Composition	mp, °C	$[\alpha]_D$, deg	Source of isolation	Literature
		IV. Clerodin group			
79. Clerodin	$C_{24}H_{34}O_7$	164-165	−47	*Clerodendron infortunatum*	9-13
80. Clerodendrin A	$C_{31}H_{42}O_{12}$	164-165	+7.4 (chl)	*Clerodendron tricotomum*	71
81. Carioptin	$C_{26}H_{36}O_9$	176-177	−91 (chl)	*Cariopteris divaricata*	72
82. Carioptinol	$C_{24}H_{34}O_8$	219-220	−83 (chl)	"	72
83. Dihydrocarioptinol	$C_{24}H_{36}O_8$	204-205	−73 (chl)	"	72
84. Substance 1	$C_{22}H_{42}O_9$	158-161	−26.8 (chl)	*Ajuga iva*	73
85. Substance 2	$C_{28}H_{42}O_{10}$	Oil	−8.0 (chl)	"	73
86. Substance 3	$C_{29}H_{44}O_{10}$	Oil	+4.1 (chl)	"	73
87. Substance 4	$C_{30}H_{46}O_{11}$	Oil	+31.7 (chl)	"	73
88. 2-Acetylivain	$C_{30}H_{44}O_{11}$	Oil	+15.9	*Ajuga pseudoiva*	74
89. Dihydroajugapitin		Oil	−41.5	"	74
90. Dihydroajugapitin	$C_{29}H_{42}O_{10}$	212-214	−40 (chl)	*Ajuga chamaepitys*	25
91. Ajugapitin	$C_{29}H_{42}O_{10}$	196-198	−70.3 (chl)	"	25
		V. Group of clerodane derivatives with aliphatic side chains			
92. Kolavenol	$C_{20}H_{34}O$	Oil (bp 140-150°)	−45.7	*Solidago elongata*	53
93. Methyl kolavenolate	$C_{21}H_{34}O_2$	Oil (bp 170-180/0.4)	−65.6	"	75
94. Methyl 6-acetoyloxykolavenolate	$C_{23}H_{36}O_4$	Oil		"	53
95. Methyl 6-angeloyloxykolavenolate	$C_{26}H_{40}O_4$	Oil		"	53
96. Kolavelool	$C_{20}H_{34}O_3$	Oil		"	53
97. 6-Angeloyloxykolavelool	$C_{25}H_{40}O_3$			"	53
98. Solidagonic acid	$C_{22}H_{34}O_4$	143-144	−97.6	*Solidago altissima*	76
99. Cistoic acid	$C_{20}H_{32}O_4$	255-256	+63.6 (ethanol)	*Cistus monspeliensis*	77
100. Haplopappic acid	$C_{20}H_{30}O_4$	242-244	+117.6	*Haplopappus foliosus*	78
101. Cistodiol	$C_{20}H_{36}O_2$	86-88	+47.9	*Cistus monspeliensis*	77
102. Component C	$C_{20}H_{32}O_2$	Oil		*Solidago serotina*	54
103. Component D	$C_{20}H_{32}O_2$	Oil		"	54
104. Component E	$C_{20}H_{32}O_2$	Oil		"	54
105. Component F	$C_{20}H_{32}O_2$	Oil		"	54
106. Diacid	$C_{20}H_{30}O_4$	199-201	−87.4 (pyridine)	*Guanostegia angustifolia*	79
107. Stachysolone	$C_{20}H_{32}O_3$	153-155		*Stachys annua*	80
108. Linaridial	$C_{20}H_{30}O_2$	Oil	+13	*Linaria japonica*	81
109. Annuanone	$C_{20}H_{32}O_3$	171-172	+25	*Stachys annua*	82
110. Floridiolic acid	$C_{20}H_{32}O_4$	130	−66 (alcohol)	*Evodia floribunda Baker*	83
111. cis-Clerodanic acid	$C_{20}H_{34}O_2$	Oil	−10	*Macowania glanduglosa*	84
112. Linarienone	$C_{27}H_{40}O_5$	Oil	+3 (chl)	*Linaria japonica*	85
113. Haplociliatic acid	$C_{20}H_{34}O_4$	198-201	−86 (alcohol)	*Haplopappus ciliatus*	86
114. Substance 1	$C_{24}H_{32}O_5$	93-94	−68	*Stachys recta*	87
115. Substance 2	$C_{22}H_{30}O_4$	Oil	−73	"	87
116. Substance 3		130-131	−45.2	"	87
117. Salvicin	$C_{20}H_{32}O_4$	157-158		*Pulicaria salviifolia*	104, 119

TABLE 1 (Continued)

Compound	Composition	mp, °C	$[\alpha]_D$, deg	Source of isolation	Literature
VI.	Clerodane diterpenoids of the hardwickiic acid group				
118. (−)-Hardwicki acid	$C_{20}H_{28}O_3$	105-107	−114.7	*Hardwickia pinnata*	75
119. (+)-Hardwicki acid	$C_{20}H_{28}O_3$	104-106	+125	*Coraifera officinalis*	88
120. Substance II	$C_{20}H_{30}O$	Oil	−32 (chl)	*Annona coriacea*	89
121. Fruticolone	$C_{22}H_{30}O_6$	150	+28.3	*Teucrium fruiticans*	48
122. Isofruticolone	$C_{22}H_{30}O_6$	Oil	−87.8	"	48
123. Bacchotricuneatin D	$C_{20}H_{30}O_3$	109-111	−7.41 (chl)	*Bacharis tricuneata*	69
124. Hautrivaic acid		179-179.5		*Dodonaea viscosa*	90
125. Acetoxyhydroxy acid I	$C_{22}H_{30}O_6$	160-162	−109	*Dodonaea attenuata*	91
126. Maingayic acid	$C_{20}H_{28}O_3$	Oil	−252 (c 3.0; chl)	*Callicarpa maingayi*	92
127. Solidagoic acid A	$C_{20}H_{28}O_3$	169-171	−58	*Solidago gigantea*	93
128. Solidagoic acid B	$C_{25}H_{34}O_5$	134-135	−28 (chl)	"	94
129. Component I	$C_{20}H_{28}O_2$	Oil	−164	*Solidago gigantea var. Serotina*	94
130. Component II	$C_{20}H_{26}O_3$	92-95	+12	"	94
131. Component III	$C_{20}H_{26}O_3$	103-105	−49	"	94
132. Component IV	$C_{20}H_{30}O_2$	Oil	−38	"	94
133. Component V	$C_{20}H_{30}O_2$	Oil	−45	"	94
134. Component VII	$C_{20}H_{28}O_4$	Oil	−47	*Solidago gigantea var. Serotina*	94
135. Component VIII	$C_{20}H_{30}O_3$	60-63	−46	"	94
136. Component IX	$C_{20}H_{30}O_5$	135-137	−18	"	94
137. 3-Hydroxyimbricatol isovalerate	$C_{25}H_{38}O_4$	103	−115	*Hinterhubera imbricata*	95
138. 3-Hydroxyimbricatol α-methylbutyrate	$C_{25}H_{38}O_4$	149	−118	"	95
139. 3-Hydroxyimbricatol angelate	$C_{25}H_{36}O_4$	80		"	95
140. Agbaninol	$C_{20}H_{30}O_2$	70-71	−4.9 (c 0.09)	*Grossweiterodendron balsamiferum*	96
141. Agbanindiol B	$C_{20}H_{30}O_3$		Amorph. +26.4 (c 0.11)	"	96
142. Junceic acid	$C_{20}H_{28}O_3$	Oil	−59	*Solidago juncea*	97
143. Juneic acid epoxide	$C_{21}H_{30}O_4$	Oil	−49	"	97
144. Component B	$C_{20}H_{30}O_2$	93-94	−19	*Solidago serotina*	54
145. Alcohol 2	$C_{20}H_{30}O_2$	138-140	−73.0	*Dodonaea boroniafolia*	98
146. Acid	$C_{20}H_{28}O_4$	Oil		"	98
147. Alcohol 1	$C_{20}H_{30}O_2$	Oil		"	98
148. Acid	$C_{20}H_{28}O_5$	185-187	−135 (methanol)	*Olearia muelleri*	99
149. Acetoxyhydroxy acid	$C_{20}H_{30}O_6$	160-162	−109	*Dodoneae attenuata var. linearis*	100
150. Dienic acid	$C_{20}H_{26}O_4$	161-163	−153	"	100
151. Component 2a	$C_{20}H_{30}O$	Oil	+33 (chl)	*Solidago arguta Ait*	26
152. Component 2b	$C_{22}H_{32}O_3$	Oil	+49 (chl)	*Solidago arguta Air*	26
153. Component 2c	$C_{20}H_{30}O_2$	Oil	+42 (chl)	"	26
154. Component 2e	$C_{22}H_{34}O_4$	Oil	+13 (chl)	"	26
155. Diol 2d	$C_{20}H_{30}O_3$	103-104	+23	"	26
156. Lactone 4	$C_{20}H_{24}O_3$	142-143	+34	"	

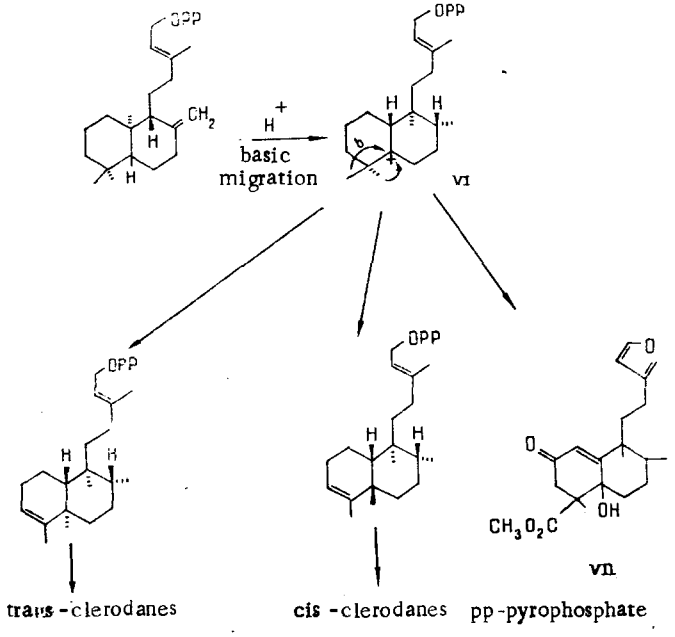
TABLE 1 (Continued)

Compound	Composition	mp, °C	$[\alpha]_D$, deg	Source of isolation	Literature
157. Bacchotricuneatin D	$C_{20}H_{30}O_3$	109-111	−7.41 (chl)	*Baccharis tricuneata*	69
158. Hardwickiic acid derivative		161	−62	*Pulicaria gnaphalodes*	24
159. 8β-Hydroxy-fruticolone	$C_{22}H_{30}O_7$	Oil		*Teucrium fruticans*	101
160. Methyl 19-O-methylhautriwate	$C_{22}H_{32}O_4$	Oil	−69, −73, −84, −149 (chl)	*Conyza scabrida*	21
161. Methyl 19-O-angeloylhautriwate	$C_{26}H_{36}O_5$	Oil		*Conyza scabrida*	21
162. Methyl 19-O-isovaleryl-hautriwate	$C_{26}H_{38}O_5$	Oil		"	21
163. Dodonic acid	$C_{20}H_{28}O_4$	93-95		*Dodonaea viscosa*	02
164. Salvin	$C_{20}H_{26}O_3$	128	−110.4 (c 0.42; methanol)	*Pulicaria salviifolia*	34, 104
165. Salvinin		127	−128 (c 0.22; methanol)	"	34, 104



IV V

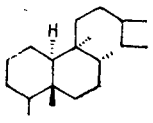
In view of the biogenetic relationship between the clerodane and the labdane diterpenoids, many authors ascribe to the clerodanes the trans-steroid type of linkage of the rings that occurs in the labdane diterpenoids. Some authors have substantiated the possibility for the clerodane diterpenoids of two types of linkage — cis and trans-steroid. According to a proposal by Wilson [28], the formation of two similar series of cis- and trans-cerodanes takes place as the result of the migration of a methyl group from a labdane precursor. For the formation of a trans-clerodane the concerted migration of methyl



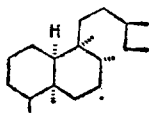
groups is necessary. However, for the formation of a cis-A/B linkage of the rings a "pause" at the ion (VI) is necessary.

On the question of the information of clerodanes with the trans- and cis-steroid type of ring linkage, Wilson writes in favor of a labdane precursor, although the figure clearly illustrates the production of the corresponding clerodanes from ent-labdanes, i.e., spatial antipodes of the labdanes with respect to the type of ring linkage.

A second series of clerodanes (VIII, IX) is formed from labdanes



VIII



IX

Almost all compounds with a strictly established absolute stereochemistry have the trans-steroid type of ring linkage.

Some authors call compounds with the trans-steroid type of ring linkage ent-labdanes [62, 69]. Recently, such compounds have more frequently been called neo-clerodanes, and their spatial antipodes with respect to the type of linkage ent-neoclerodanes [119].

The question of determining the type of ring linkage is almost the most complicated in the whole stereochemistry of the clerodane diterpenoids and is most frequently solved only by x-ray structural analysis [12, 38, 105].

At the present time, the linkage of the rings is determined fairly frequently on the basis of the results of circular dichroism by comparison with the CD spectra of compounds with known stereochemistry. This method has been used particularly widely for determining ring linkage in the teucrins [29-33]. But when CD results are used a certain degree of caution is necessary, since, according to modern ideas, for many clerodane diterpenoids the ring linkage cannot be regarded as having been reliably established.

In connection with the appearance of high-resolution PMR spectrometers, without the performance of supplementary chemical transformations and, in particular, allyl oxidation (cases are known of the allyl bromination of salvin, salvifolin, and the methyl ether of salvifolin) [34], the possibility has arisen of detecting the signal of the proton at C-10 and calculating its splitting constant. But it is impossible to determine ring linkage unambiguously from splitting constants.

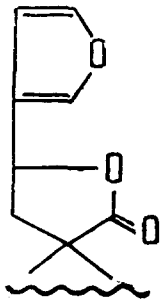
In the clerodane diterpenoids, the double bonds are located both in the cyclic part of the molecule and in the side chain. Characteristic for the cyclic part of the molecule is the presence of a double bond at C_3—C_4 [20, 53, 55, 58, 61, 62] or, for 19-nor-compounds, at C_4—C_5 [29, 30, 31, 35, 42]. But the double bond may be located between other carbon atoms although this is the case far more rarely. A striking feature of these diterpenoids is the diversity of the oxidized molecules: oxygen functions are found both in the nucleus and in the side chain. It is interesting that the degree of oxidation of the side chain includes the formation of a furan ring.

In the clerodane diterpenoids, ester groups, hydroxy groups of primary, secondary, and tertiary nature, and also epoxide rings and ether bridges are found, but the most characteristic fragments of the structure are γ-lactone rings and carboxy groups [28, 67, 68-72]. As a rule, the addition of a lactone ring takes place at the fourth and fifth carbon atoms of the main skeleton. Sometimes linkage is effected with the fourth and sixth carbon atoms, but this variant is found fairly rarely and is characteristic mainly for substances isolated from plants of the genus *Teucrium* (family Labiatae) [29, 31, 35, 39]. In the clerodane diterpenoids, carboxy groups are located at the fourth carbon atom, as is cistoic (99) [77], haplopappic (100) [78], and floribundic (72) [68] acids. But cases are known of the attachment of the carboxy group to the fifth carbon atom, as in maingayic acid (126) [92] and solidagoic acid B (128) [93]. Cases are also known of the attachment of a carboxy group to the side chain [32, 33, 80, 86].

There are ester functions in kolavelool (96), 6-angeloyloxykolavelool (97) [53], elongatolides B, C, D, and E (40-42) [53], solidagoic acid B (128) [93], and 3-hydroxyimbricatol isovalerate (137) [95]. But ester groups, especially acetyl groups, are found particularly frequently in diterpenoids of the clerodin type [72, 73].

In view of the considerable development of the chemistry of the clerodane diterpenoids in recent years and the accumulation of a large amount of factual material, the problem of the classification is becoming more and more urgent. A detailed analysis that we have made has shown that it is most desirable to classify the clerodanes according to the type of structure of the side chain, which contains six carbon atoms. We have divided all diterpenoids of established structure known at the present time (according to information at February, 1985, there were 165 of them) into six groups. The name of each group is derived from its parent.

To the first group must be assigned the teucrins, containing in the side chain a so-called furolactone grouping which includes a furan and a γ-lactone ring linked in such a way that the ester oxygen of the lactones is in the allyl position with respect to the furan ring (X). Mnatsaknyan has given a definition of the teucrins as substances characterized by the presence of a C_{17}—C_{12} lactone, a C_{20}-methyl group, and a furan ring at C_{12} formed by the C_{13}, C_{14}, C_{15}, and C_{16} atoms of the clerodane system [103]. In this group of diterpenoids in the process of biogenesis in a plant a methyl group is eliminated and a series of compounds of norclerodane nature is formed [50, 51, 53, 62].

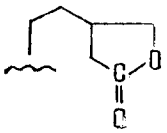


X

In some teucrins, the oxygen of the lactone function forms with the carbon atoms of the main skeleton an epoxide ring, as in salvifarin (15), salvifaricin (16) [40], teupyrenone (22) [43], and teucrin P (8) [32].

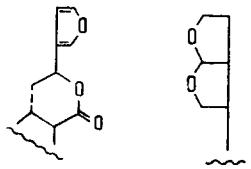
In the last 5-10 years, the chemistry of the teucrins has developed at particularly fast rates, thanks mainly to the work of G. Savona, F. Piozzi, and B. Rodriguez (Spain) and of P. Malakov and G. Pananov (Bulgaria). The teucrins form the only group of clerodane diterpenoids several representatives of which have been isolated from plants of the USSR flora by Soviet workers (D. P. Pop and A. M. Reinbol'd, and G. B. Oganesyan and V. A. Mnatsaknyan) [29, 30, 32, 42, 56, 82]. At the present time, the teucrins form the largest group of clerodane diterpenoids, numbering 38 compounds.

The second group of clerodane diterpenoids includes the elongatolides, containing a γ-lactone ring in the side chain (XI). Elongatolide derivatives were first detected in plants of the genus *Solidago* (family Asteraceae), they have also been isolated mainly from representatives of the genera *Leonurus*, *Chaiturus*, and *Ajuga* (family Labiatae) [53-57].



XI

The columbins belong to a third group of substances in which a δ-lactone grouping in the side chain is condensed with ring B of the main skeleton and is linked by a carbon-carbon bond with a β-substituted furan ring (XII). The first representative of this series of substances was columbin (63), the structure of which was established more than half a century ago and has been the object of disputes and revisions. A definitive conclusion was made with the aid of x-ray structural analysis [105]. The columbin group includes tinophyllone (68) [65], fibleucin (69) [66], fibraurin (70) [67], and floribundic acid (72) [68], which have been isolated from tropical plant species. Representatives of the genus *Baccharis* that are known in folk medicine for their antimicrobial and antitumoral action also produce mainly substances of the columbin group [62, 69].



XII XIII

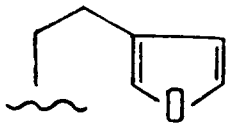
The fourth group of clerodane diterpenoids includes the clerodins. Their side chain contains condensed tetrahydrofuran rings (XIII). Compounds of the clerodin group are extremely labile and are produced mainly by plants of the family Verbenaceae.

Clerodin (79) the parent of this group of substances, was isolated from *Clerodindron infortunatum* in 1936. Its structure and stereochemistry were definitively established in 1961 on the basis of an x-ray structural analysis of its bromolactone. Characteristic for the clerodins is the presence of epoxide rings and acetyl ester groupings [53, 73-75, 95].

We have also separated out an individual group of clerodane diterpenoids with an aliphatic side chain. These include derivatives of kolavenic acid (93-95) [53], cistodiol (101) [77], haplopappic acid (100) [78], stachysolone (107) [80], and annuanone (109) [82].

As a rule the aliphatic side chain is highly oxidized and, in particular, contains an alcoholic hydroxyl, as in cistodiol (101) [77], and floridiolic acid (110) [83], an aldehyde group — in the components of *Solidago serotina* [102-105] [54], or carboxy groups — in cistoic acid (99) [77] and the ent-clerodanic acid from *Guanostegia angustifolia* (106) [79]. Sometimes the side chain contains an ester grouping, as in linarienone (112) [85].

The last, sixth, group of clerodane terpenoids is formed of derivatives of hardwickiic acid in which the unsubstituted side chain is terminated by a furan ring (XIV).



XIV

The parents of these compounds are the (+)- and (−)-hardwickiic acids (118 and 119) isolated from the *Hardwickia pinnata* and *Coraifera officinalis* [75, 88]. The absolute configuration of hardwickic acid has been established by a series of transformations and by comparison of the CD spectra of the products obtained with those of known compounds [106, 107].

METHODS OF ISOLATING AND DETERMINING THE STRUCTURES OF THE CLERODANE DITERPENOIDS

At the present time, the search for clerodane diterpenoids is promising not only among plants of the family Labiatae but also among such widespread families as Rutaceae, Verbenaceae, Menispermacrae, Euphorbiaceae, and, finally, Asteraceae. Clerodane diterpenoids have also been detected in plants of the tropical zone (family Caesalpinaceae). The material of investigation is mainly the roots and epigeal organs of the plant, the amount of the substances in lignified stems being small.

Extraction is carried out with chloroform and with ethyl acetate and, more rarely with alcohol, acetone, ether, and, sometimes, hexane.

Chromatography is performed on columns containing silica gel or silica gel impregnated with $AgNO_3$ and, more rarely, on neutral alumina. The polar fractions are frequently methylated, and then the methyl esters are chromatographed. The yields of substances range within wide limits — from minor amounts to 0.6% (solidagoic acid A (127) from *Solidago gigantea*) [93].

The elementary compositions of the diterpenoids are determined analytically or, recently, more and more frequently by high-resolution mass spectrometry. PMR spectroscopy provides the possibility of determining the presence of two tertiary and one secondary methyl groups which, in combination with the elementary composition of the substance permit its

unambiguous assignment to the clerodane diterpenoids. The signals of the methyl groups are usually found for the C_{17} and C_{20} methyls at from 0.7 to 1.2 ppm, and for the C_{19} methyl at from 1.00 to 1.2 ppm.

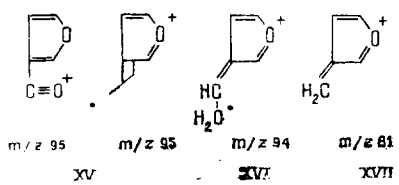
Previously, to establish the type of carbon skeleton of a bicyclic diterpenoid wide use was made of the dehydrogenation reaction, which is carried out by heating the substance with such catalysts as sulfur, selenium, and palladium on carbon. For bicyclic diterpenoids the most suitable catalyst is selenium, which is characterized by a mild action and excludes possible rearrangements. With this catalyst the lactone ring is opened and a hydrocarbon is formed which contains one carbon atom less than the initial compound. Angular methyl and hydroxy groups are readily eliminated while ester groups are not affected by the dehydrogenation reaction [93]. But it is frequently impossible to distinguish clerodane and labdane diterpenoids from the products of the dehydrogenation reaction, since, depending on the structure of the compounds and the conditions of the reaction, they may give identical products [17].

At the present time, the dehydrogenation reaction has lost its primary importance because of the small amounts of substances isolated from plants and the difficulties of interpreting the results obtained.

A feature of clerodane diterpenoids is the C_3—C_4 double bond. In the PMR spectrum, the signal of the olefinic proton appears in the form of a triplet [75] or, sometimes, a multiplet at 6.2-6.7 ppm [26]. Depending on stereochemical factors and, in particular, on the nature of the linkage of the rings, this double bond is reactive to different degrees. Palladium on carbon and Adams catalyst are used for its hydrogenation. Sometimes, hydrogenation at the C_3—C_4 double bond is difficult even in acetic acid with the use of platinum dioxide as catalyst [34, 104]. In certain cases, sodium in ethanol is used as the reducing agent [91].

One of the characteristic functional groups in the clerodane diterpenoids is a furan ring, which is detected from the pink coloration with the Ehrlich reagent [108]. To prove the presence of a furan ring chemically it is possible to obtain the adduct with maleic anhydride, but this reaction is not always feasible. In the UV spectrum a furan ring gives a band at 210-220 nm. Depending on the number of chromophores and their nature, absorption may be detected within the range up to 250 nm. When the carbonyl group is conjugated with an ethylene link, the absorption band of the furan and the ethylene groups may coincide and sometimes also be split [75]. In the IR spectrum, four bands correspond to a furan ring: 1) a weak band at 3165-3125 cm^{-1}; 2) a band of variable intensity between 1580 and 1500 cm^{-1}; 3) the most characteristic band at 885-870 cm^{-1}; and 4) a broad, frequently split, band at 800-740 cm^{-1} [109]. In characterizing a furan ring, reference is made to the second and third bands or sometimes only to the third [68, 110].

Mass spectra play an important role in the investigation of the clerodanes. Analysis of the mass spectra, particularly, the high-resolution spectra permits the molecular weight to be determined and the number and nature of the functional groups to be revealed. Under the action of electron impact, the clerodanes, like other compounds, form fragments corresponding to the splitting out of one or more water molecules, methyl groups, and the side chains. For example, the presence in the mass spectrum of a substance of peaks with m/z 94, 95, and 81 unambiguously shows that the molecule contains a furan ring, and from the relative intensities of these peaks it is possible to judge the nature of the side chain. Fragment (XVII) predominates in the spectra of furan derivatives with an unsubstituted side chain, and the ions (XV) and (XVI) give peaks of greater intensity in the case of lactones such as the bacchotricuneatins [28, 65, 67, 69].



XV XVI XVII

The nature of an oxygen function in the side chain can be judged from whether the cleavage of the chain takes place between C_9 and C_{11} or between C_{11} and C_{12} [53, 93].

In the PMR spectrum, the protons of the furan nucleus give three signals in the weak-field region resembling the signals of aromatic protons [44, 101].

In contrast to a double bond in the main skeleton, double bonds of the furan ring are very reactive, and the conversion of the furan ring into a tetrahydrofuran ring takes place in the presence of ordinary hydrogenation catalysts. In the spectrum of the reduced product, while the triplet of the H-3 olefinic proton is retained, the signal of the protons of the furan ring has disappeared.

It was mentioned above that the presence of carboxy and lactone groupings is characteristic for the main skeleton of the clerodane diterpenoids, and these are easily detected from the characteristics of the IR spectrum. As is well known, the most specific feature of γ-lactones is their capacity for opening under treatment with alkali with the formation of salts of hydroxy acids the acidification of which re-forms the γ-lactones. However, the formation of the initial substances is not always possible for several reasons. Thus, for example, if there is a hydroxy group in a neighboring position to the lactone ring, the closure of the lactone ring in the other direction (the production of allo compounds) is possible. If in the α-position to the hydroxy group formed after the opening of the lactone ring there is a double bond, dehydration takes place. Cases have been described in the literature of the formation of oxides as the result of the interaction of a hydroxy group with a double bond [111]. Hydroxy acids may ring-close in the presence of lactonization reagents such as N,N-dicyclohexylcarbodiimide.

Reducing agents for reducing a carbonyl group are diisobutylaluminum hydride and lithium tetrahydroaluminate. In these cases, ester and ketone groups are reduced to the corresponding carbinols. Olefinic bonds usually remain unaffected in this reaction, but because of conjugation with the carbonyl group a C-3 olefinic bond may be hydrogenated.

Sometimes sodium in ethanol is used as the reducing agent, but in this case several side reactions take place simultaneously which complicates the interpretation of the results obtained. For example, in the case of a compound from *Dodonaea attenuata* [91], sodium in ethanol, in addition to reducing the C-3 olefinic bond, acted as a lactonization reagent. Simultaneously with this, the alkaline medium created by the products of the main reaction led to the saponification of the ester grouping of the side chain.

Recently, to answer questions of structure, wider and wider use has been made of ^{13}C NMR spectroscopy. As applied to the clerodane diterpenoids, this method has been developed in [19, 39-42, 47, 48, 110]. The multifrequency resonance and INDOR methods are often used for structural investigations in the chemistry of the clerodane diterpenoids [46, 87, 24]. To determine the spatial positions of functional groups use is made of the nuclear Overhauser effect, with the aid of which protons not interacting through a system of bonds but spatially close (<3 Å) protons are detected [76, 87]. Conformational features of clerodanes have been elucidated with the aid of x-ray structural analysis [48, 58, 79, 110, 112].

BIOLOGICAL ACTIVITY

The interest in the clerodane diterpenoids is due to their biological activity. Although the clerodanes belong to a new group of natural isoprenoids, their pharmacological action has been studied fairly fully. On the basis of the material that we have analyzed it appears possible to make some correlations between the structure of the substances, the type of plants producing these compounds, and the nature of their action.

For example, the clerodanes isolated from plants of the family Verbinaceae are known as insect antifeedants [25, 71]. Antimicrobial activity has been described for compounds of the columbin group produced only by plants of the genus *Bacharis* [113-115].

The teucrins posses antitumoral and cholagogic activity, and recently investigations of their cardiotonic and coronarodilating activity have been made on the basis of teucrins H_1-H_4 [115, 116]. Characteristic for maingayic acid is a high pesticidal activity, which has led to the development by several groups of workers of synthetic methods for its production [117, 118].

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