PROGRESS IN THE CHEMISTRY OF THE CYCLOARTANES

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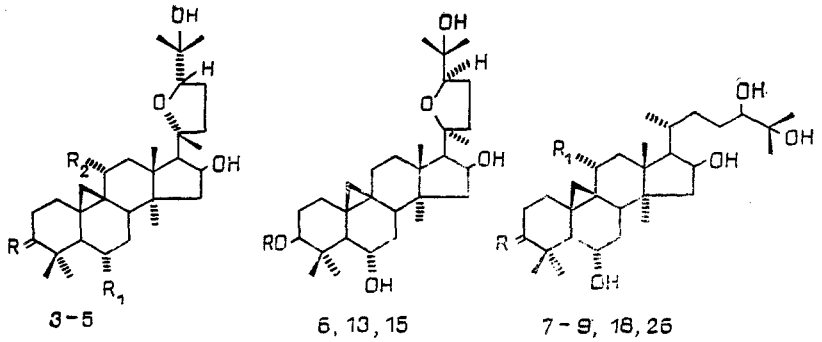
The review, which considers advances in the chemistry of the cycloartanes, covers literature devoted to compounds of plants of the genus Astragalus and other publications appearing in the period from 1984 to 1987 and, in part, 1988.

Until recently, interest in the cycloartanes was due to the fact that the initial compound of this series – cycloartenol – was a key intermediate in the biosynthesis of phytosteroids. In recent years, cycloartanes have attracted the attention of research workers not only as substances promoting our understanding of the pathways of the biosynthesis of phytosteroids and the discovery of new ones but also as compounds possessing a broad spectrum of biological activity. This circumstance has predetermined the growing rate of investigations in the field of the chemistry and biology of the cycloartanes. The increasing interest in these compounds can be clearly traced from the fact that while in the middle of the 70s, i.e., 25 years after the structure of cycloartenol had been established, about 50 derivatives were known, by the beginning of 1984 this number had risen to more than 160 [1], and at the present time the number of compounds of this class that have been described has surpassed 200. In parallel, the number of publications on biological investigations of the cycloartanes has also increased. Progress has been reported in the study of the glycosylated forms of the compounds under consideration. As a rule, the polyhydroxy compounds are found in the form of glycosides. The spectrum of the distribution of the polyhydroxycycloartanes and their glycosides is narrower than that of the weakly polar cycloartanes that are found mainly in plants belonging to six families: Leguminosae, Ranunculaceae, Combretaceae, Passifloraceae, Meliaceae, and Orchidaceae.

The present review considers advances in the chemistry of the cycloartane methylsteroids and covers the literature devoted to the cycloartanes of plants of the genus Astragalus and other publications that have appeared since our first review [1].

The investigation of the secondary metabolites of representatives of the broad genus Astragalus was limited mainly to phenolic compounds until publications [2-5] appeared which showed that the plants of this genus produced cycloartanes. Compounds of the series under consideration isolated from plants of the genus Astragalus are shown in Scheme 1, and the physicochemical constants of these substances are given in Table 1. Table 2 includes the free cycloartanes and their glycosides, and also their 4-monomethyl and 4,4-demethyl analogs, from other sources. Scheme 2 shows their structural formulas.

Scheme 1



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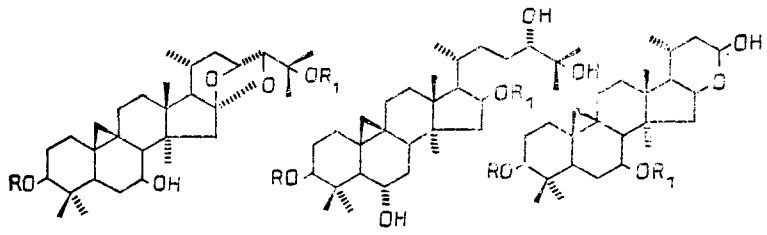
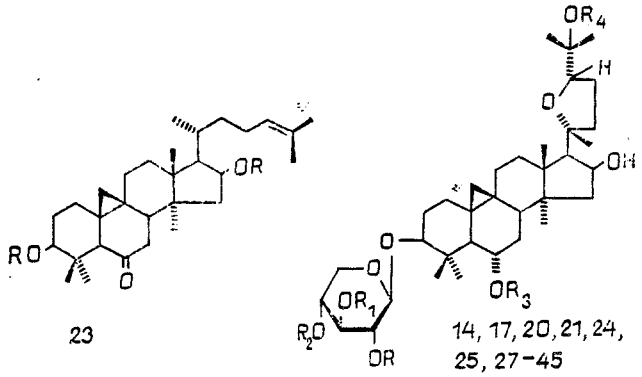
Scheme 1 (continued)



2, 12, 19 10, 22 1, 11, 16



23 14, 17, 20, 21, 24, 25, 27–45

1. R=R_1=H
2. R=R_1=H
3. R=O, R_1=R_2=OH
4. R=  , R_1=R_2=H
5. R=  , R_1=OH, R_2=H
6. R=H
7. R=O, R_1=OH
8. R=O, R_1=OH
9. R=  , R_1=H
10. R=R_1=H
11. R=β-*D*-Xylp, R_1=H
12. R=β-*D*-Xylp, R_1=H
13. R=β-*D*-Xylp
14. R=R_1=R_2=R_3=R_4=H
15. R=β-*D*-(2-OAc)-Xylp
16. R=β-*D*-Xylp, R_1=β-*D*-Glcp
17. R=R_1=R_2=R_4=H, R_3=β-*D*-Xylp
18. R=  , R_1=H
19. R=β-D-Xylp, R_1=β-*D*-Glcp
20. R=R_1=R_2=R_4=H, R_3=β-*D*-Glcp
21. R=β-*D*-Glcp, R_1=R_2=R_3=R_4=H
22. R=β-*D*-Xylp, R_1=β-*D*-Glcp
23. R=β-*D*-Glcp
24. R=Ac, R_1=R_2=R_4=H, R_3=β-*D*-Xylp
25. R_1=Ac, R=R_2=R_4=H, R_3=β-*D*-Xylp
26. R=, R_1=H
27. R=Ac, R_1=R_2=R_4=H, R_3=β-*D*-Glcp
28. R_1=Ac, R=R_2=R_4=H, R_3=β-*D*-Glcp
29. R=R_1=Ac, R_2=R_4=H, R_3=β-*D*-Xylp
30. R=R_2=Ac, R_3=β-*D*-Xylp, R_1=R_4=H
31. R=R_1=Ac, R_2=R_4=H, R_3=β-*D*-Glcp
32. R=R_2=Ac, R_1=R_4=H, R_3=β-*D*-Glcp
33. R=α-*L*-Arap, R_1=R_2=R_4=H, R_3=β-*D*-Xylp
34. R=R_1=R_2=Ac, R_3=β-*D*-Xylp, R_4=H
35. R=α-*L*-Rhap, R_1=R_2=R_4=H, R_3=β-*D*-Glcp
36. R=R_1=R_2=Ac, R_4=H, R_3=β-*D*-Glcp
37. R=α-*L*-Arap, R_1=Ac, R_2=R_4=H, R_3=β-*D*-Xylp
38. R=α-*L*-Rhap, R_1=R_2=R_4=H, R_3=β-*D*-Glcp
39. R=R_3=β-*D*-Glcp, R_1=R_2=R_4=H
40. R=R_1=R_2=H, R_3=R_4=β-*D*-Glcp
41. R=R_4=β-*D*-Glcp, R_1=R_2=R_3=H
42. R=α-*L*-Rhap, R_1=Ac, R_2=R_4=H, R_3=β-*D*-Xylp
43. R=α-*L*-Rhap, R_2=Ac, R_1=R_4=H, R_3=β-*D*-Xylp
44. R=α-*L*-Rhap, R_1=Ac, R_2=R_4=H, R_3=β-*D*-Glcp
45. R=α-*L*-Rhap, R_2=Ac, R_1=R_4=H, R_3=β-*D*-Glcp

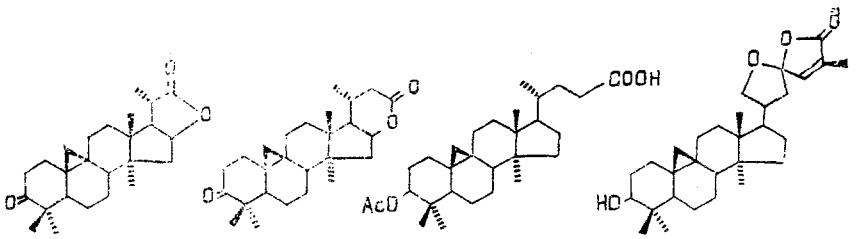
TABLE 1. Cycloartane Methylsteroids and Their Glycosides from Plants of the Genus Astragalus

Name, synonyms, molecular formula	mp, °C $[\alpha]_D$, degrees (solvent)	Species of milk vetch	Literature
1	2	3	4
1. Dasyanthogenin $C_{26}H_{42}O_4$	210—214; 0 (ethanol)	A. dasyanthus Pall.	3
2. Cycloorbigenin $C_{30}H_{48}O_5$	217—219; +28,3 (ethanol)	A. orbiculatus Ledeb.	13
3. Cycloasgenin A $C_{30}H_{48}O_6$	235—236; +130 (methanol)	A. taschkendicus Bunge.	4
4. Quisquagenin $C_{30}H_{50}O_4$	232,5—234,5; +36,6 (chloroform)	A. quisqualis Bunge	14
5. Cyclosieversigenin $C_{30}H_{50}O_5$ (cycloastragenol, astramembrangenin)	239—241; +50,6 (methanol)	A. sieversianus Pall. A. taschkendicus Bunge, A. membranaceus Bunge, A. pamirensis Ovcz. et Rassulova, A. pterocephalus Bunge, A. tragacantha Habl., A. mongholicus Bunge.	2, 6—8, 10—12, 15, 16 90
6. Cyclogalegigenin $C_{30}H_{50}O_5$	195—196; +28,7 (methanol)	A. galegiformis L.	7—9
7. 3-Dehydrocycloasgenin C $C_{30}H_{50}O_5$	208—210; +82,5 (methanol)	A. taschkendicus Bunge	17
8. Cycloasgenin B $C_{30}H_{50}O_6$	232—233; +98,9 (methanol)	A. taschkendicus Bunge	18
9. Cycloasgenin C $C_{30}H_{52}O_5$	244—246; +33,7 (methanol)	A. taschkendicus Bunge	6
10. Cyclocanthogenin $C_{30}H_{52}O_5$	194—195; 57,5 (methanol)	A. tragacantha Habl.	16
11. Dasyanthoside B $C_{31}H_{50}O_8$	255—260; —20 (methanol)	A. dasyanthus Pall.	19
12. Cycloorbicoside A $C_{35}H_{56}O_9$	267—269; +8,3 (methanol)	A. orbiculatus Ledeb.	20
13. Cyclogaleginoside B $C_{35}H_{58}O_9$	252—254; +32 (pyridine)	A. galegiformis L.	21
14. Cyclosieversigenin 3-O-β-D-xylopyranoside $C_{35}H_{58}O_9$ (astramembranin II)	263—264; +41,5 (methanol)	A. pamirensis Ovcz. et Rassulova, A. membranaceus Bunge, A. tragacantha Habl.	15, 22, 32
15. Cyclogaleginoside A $C_{37}H_{60}O_{10}$	224—226; +40 (pyridine)	A. galegiformis L.	21
16. DasyanthosideA $C_{37}H_{60}O_{15}$	204—208; 265—267; —15 (methanol)	A. dasyanthus Pall.	19
17. Cyclosieversioside E $C_{40}H_{68}O_{13}$ (astrasieversianin X)	218—220; +29,9 (methanol)	A. sieversianus Pall., A. pterocephalus Bunge, A. schachirudensis Bunge, A. basineri Trautv.	15, 23—26
18. Askendoside C $C_{40}H_{68}O_{13}$	197—198; +27,3 (methanol)	A. taschkendicus Bunge	27
19. Cycloorbicoside G $C_{41}H_{68}O_{14}$	247—249; 0 (methanol)	A. orbiculatus Ledeb.	28
20. Cyclosieversioside F $C_{41}H_{68}O_{14}$ (astragaloside IV, astrasieversianin XIV, astramembranin I).	284—286; +38,1 (methanol)	A. sieversianus Pall., A. membranaceus Bunge, A. pterocephalus Bunge, A. schachirudensis Bunge, A. kuhitangi (Nevski) Boriss., A. basineri Trautv., A. tragacantha Habl., A. mongholicus Bunge	7, 15, 16, 22, 24—26, 29, 30, 90
21. Astragaloside III $C_{41}H_{68}O_{14}\cdot H_2O$	245—247: +21,4 (methanol)	A. membranaceus Bunge	31
22. Cyclocanthoside D $C_{41}H_{70}O_{14}$	290—292; +9,3 (pyridine)	A. tragacantha Habl.	32
23. 6-Oxocycloartane 3β,16β-diglucoside $C_{42}H_{68}O_{13}$		A. trigonus	33
24. Cyclosieversioside C $C_{42}H_{68}O_{14}$ (astrasieversianin VI)	253—255; +30,1 (methanol)	A. sieversianus Pall., A. basineri Trautv., A. schachirudensis Bunge	24—26, 34
25. Astrasieversianin V $C_{42}H_{68}O_{14}$	233—234; +12,6 (methanol)	A. sieversianus Pall.	26

TABLE 1 (continued)

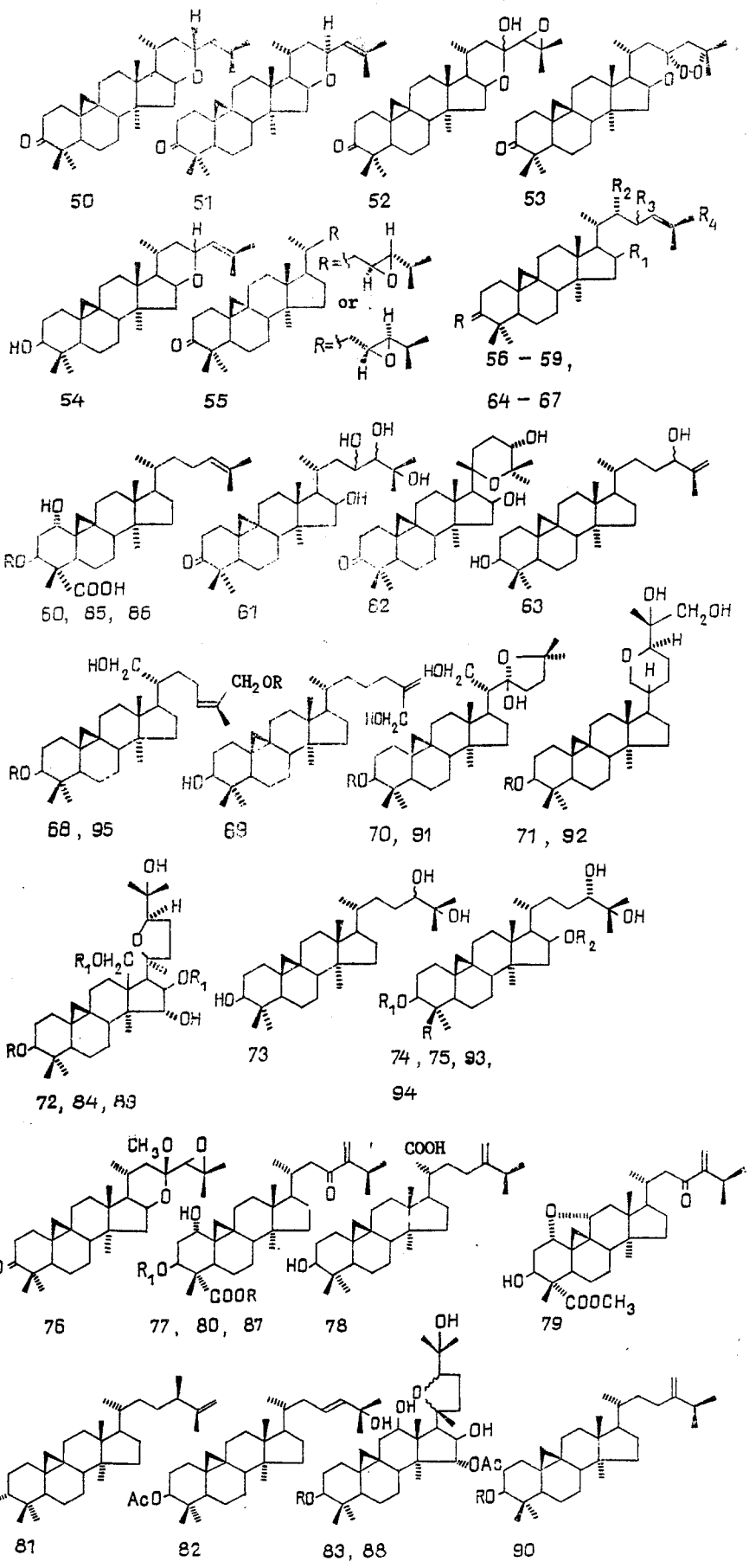
1	2	3	4
26. Askendoside A $C_{42}H_{70}O_{14}$	213-214; 0 (methanol)	A. taschkendicus Bunge	35
27. Cyclosieversioside D $C_{43}H_{70}O_{15}$ (astragaloside II and astrasieversianin VII)	254—257; +31,3 (methanol)	A. sieversianus Pall. A. basineri Trautv., A. membranaceus Bunge, A. schachirudensis Bunge, A. mongholicus Bunge.	24—26, 30, 90
28. Isoastragaloside II $C_{43}H_{70}O_{15}\cdot H_2O$ (astrasieversianin VIII)	223—224; +15,0 (methanol)	A. membranaceus Bunge, A. sieversianus Pall.	26, 30
29. Cyclosieversioside A $C_{44}H_{70}O_{15}$ (astrasieversianin II)	230—232; +23,8 (methanol)	A. sieversianus Pall., A. basineri Trautv., A. schachirudensis Bunge	24—26, 34
30. Astrasieversianin III $C_{44}H_{70}O_{15}\cdot H_2O$	250—254; +15,7 (methanol)	A. sieversianus Pall.	26
31. Cyclosieversioside B $C_{45}H_{72}O_{16}$ (astragaloside I, astrasieversianin IV)	185—188; +16,6 (methanol)	A. sieversianus Pall., A. basineri Trautv., A. membranaceus Bunge, A. schachirudensis Bunge	24—26, 30
32. Isoastragaloside I $C_{45}H_{72}O_{16}\cdot H_2O$	218—220; +17,9 (methanol)	A. membranaceus Bunge	30
33. Askendoside D $C_{45}H_{74}O_{17}$	235-236; —9,1 (pyridine)	A. taschkendicus Bunge	36
34. Astrasieversianin I $C_{46}H_{72}O_{16}\cdot\frac{1}{2}H_2O$	236—237; +5,3	A. sieversianus Pall.,	26
35. Cyclosieversioside G $C_{46}H_{76}O_{17}$ (astrasieversianin XV)	222—224; —5,42 (methanol)	A. sieversianus Pall.	37, 38
36. Acetylastragaloside I $C_{47}H_{74}O_{17}$	280—281; +1,8 (methanol)	A. membranaceus Bunge	30
37. Askendoside B $C_{47}H_{76}O_{18}$	215—218; —45,5 (pyridine)	A. taschkendicus Bunge	39
38. Cyclosieversioside H $C_{47}H_{78}O_{18}$ (astrasieversianin XVI)	262—264; —30,0 (methanol)	A. sieversianus Pall.	26, 40
39. Astragaloside VI $C_{47}H_{78}O_{19}\cdot H_2O$	290—291; +17,3 (methanol)	A. membranaceus Bunge	31
40. Astragaloside VII $C_{47}H_{78}O_{19}\cdot 2H_2O$	292—293; +10,3 (methanol)	A. membranaceus Bunge	41
41. Astragaloside V $C_{47}H_{78}O_{19}\cdot 3H_2O$	202—204; +7,2 (methanol)	A. membranaceus Bunge	31
42. Astrasieversianin IX $C_{48}H_{78}O_{18}$	208—209; —6,5 (methanol)	A. sieversianus Pall.	38
43. Astrasieversianin XI $C_{48}H_{78}O_{18}$	192—193; —9,0 (ethanol)	A. sieversianus Pall.	38
44. Astrasieversianin XII $C_{49}H_{80}O_{19}\cdot H_2O$	235—237; —4,0 (methanol)	A. sieversianus Pall.	26
45. Astrasieversianin XIII $C_{49}H_{80}O_{19}\cdot 1\frac{1}{2}H_2O$	223—225; —6,3 (methanol—water)	A. sieversianus Pall.	26

Scheme 2

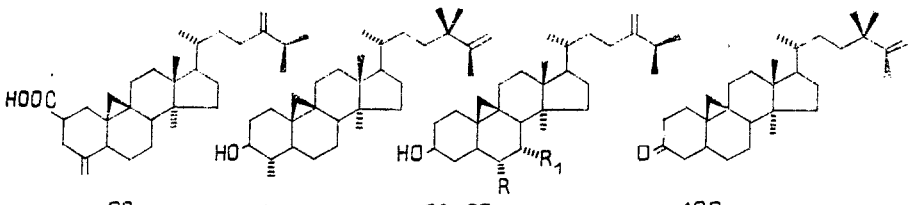


46 47 48 49

Scheme 2 (continued)



Scheme 2 (continued)



96 97 98, 99 100

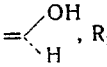
56. R=O, R_1=R_3=H, R_2=OH, R_4=CH_3
57. R=O, R_1=OH, R_2=R_3=H, R_4=CH_3
58. R=O, R_1=R_2=OH, R_3=H, R_4=CH_3
59. R=O, R_1=R_3=OH, R_2=H. R_4=CH_3
60. R=H
64. R =  , R_1=R_3=H, R_2=OH, R_4=CH_3
65. R=  , R_1=OH, R_2=R_3=H, R_4=CH_3
66. R=  , R_1=R_2=R_3=H, R_4=CH_2OH
67. R=  , R_1=R_2=OH, R_3=H, R_4=CH_3
68. R=H
70. R=H
71. R=H
72. R=R_1=H
74. R=CH_3, R_1=R_2=H
75. R=CH_2OH, R_1=R_2=H
77. R=R_1=H
80. R=CH_3, R_1=H
83. R=H
84. R=H, R_1=Ac
85. R=α-*L*-Arap
86. R=β-*D*-Xylp
87. R=H, R_1=α-*L*-Arap
88. R=β-*D*-Xylp
89. R=β-*D*-Xylp, R_1=Ac
90. R=—CO—CH=CH—C_6H_4—OH(p)
91. R=β-*D*-Glcp $\overset{6}{\leftarrow}$ β-*D*-Glcp
92. R=β-*D*-Glcp $\overset{6}{\leftarrow}$ β-*D*-Glcp
93. R=CH_3, R_1=α-*L*-Arap, R_2=β-*D*-Glcp $\overset{6}{\leftarrow}$ α-*L*-Rhap
94. R=CH_2OH, R_1=α-*L*-Arap, R_2=β-*D*-Glcp $\overset{6}{\rightarrow}$ α-*L*-Rhap
95. R=β-*D*-Glcp $\overset{6}{\leftarrow}$ α-*D*-Glcp
98. R=H, R_1=OH
99. R=OH, R_1=H

TABLE 2. Cycloartane Methylsteroids and Their Glycosides from Other Sources

Name and molecular formula	mp, °C; $[\alpha]_D$, degrees (solvent)	Source (family)	Literature
1	2	3	4
46. (16S)-23,24,25,26,27-Pentanorcycloartan-3-on-16,22-olide $C_{25}H_{36}O_3$	228—231; —	Lindheimera texana Gray et Engelm (Asteraceae)	42
47. 24-Norcycloartan-3-on-16β,23-olide $C_{26}H_{38}O_3$	229—230; —	Viguiera dentata (Asteraceae)	43
48. Trisnorcycloartanolic acid acetate $C_{29}H_{46}O_4$	219—221; —	Artemisia rubripens Nakai (Asteraceae)	44
49. Uvariastrol $C_{30}H_{44}O_4$	270; —17,5	Uvariastrum zenkeri (Annonaceae)	45
50. (16S,23R)-16,23-Epoxycycloart-24-en-3-one $C_{30}H_{46}O_2$	160—162, 5; —	Lindheimera texana Gray et Engelm. (Asteraceae)	42
51. (16S,23S)-16,23-Epoxycycloart-24-en-3-one $C_{30}H_{46}O_2$	—	Lindheimera texana Gray et Engelm. (Asteraceae)	42
52. (16β,23:24S,25-Diepoxy-23-hydroxycycloartan-3-one (23-epimers) $C_{30}H_{46}O_4$	164—167 —	Viguiera dentata (Asteraceae)	43
53. (16S,23R)-16,23-Epoxy-23,25-epidioxycycloartan-3-one $C_{30}H_{46}O_4$	214 217 —	Lindheimera texana Gray et Engelm (Asteraceae)	42

TABLE 2. (continued)

1	2	3	4
54. (3S,16S,23S)- and (3S,16S,23R)-16,23-epoxycycloart-24-en-3-ol (in a 1:2 mixture) $C_{30}H_{48}O_2$	— —	Lindheimera texana Gray et Engelm. (Asteraceae)	42
55. (16S,23S,24R)- or (16S,23R,24S)-23,24-epoxy-16,25-dihydroxycycloartan-3-one $C_{30}H_{48}O_2$	185—187 —	Lindheimera texana Gray et Engelm. (Asteraceae)	42
56. 22R-Hydroxycycloartenone $C_{30}H_{48}O_2$	Oil +27 (chlorofrom)	Balsamorhiza sagittata (Push.) Nutt. (Asteraceae)	46
57. 16S-Hydroxycycloartenone $C_{30}H_{48}O_2$	169; +27 (chloroform)	Balsamorhiza sagittata (Push.) Nutt. (Asteraceae)	46
58. 16S,22R-Dihydroxycycloartenone $C_{30}H_{48}O_3$	198; −5 (chloroform)	Balsamorhiza sagittata (Push.) Nutt. (Asteraceae)	46
59. 16S,23ξ-Dihydroxycycloartenone $C_{30}H_{48}O_3$	196; —	Balsamorhiza sagittata (Push.) (Asteraceae)	46
60. Mollic acid $C_{30}H_{48}O_4$	210—212; +61,9 (pyridine)	Combretum molle (Combretaceae)	47
61. (16S,23ξ,24ξ)-16,23,24,25-Tetrahydroxycycloartan-3-one $C_{30}H_{48}O_4$	225—228;	Lindheimera texana Gray et Engelm. (Asteraceae)	42
62. Fruticin B $C_{30}H_{48}O_4$	235—236; +12,9 (chloroform)	Parthenium fruticosum (Asteraceae)	48
63. Cycloart-25-ene-3β,24-diol (24-epimers) $C_{30}H_{50}O_2$	— —	Euphorbia trigona Haw. (Euphorbiaceae) Mangifera indica L. (Anacardiaceae)	49, 50
64. 22R-Hydroxycycloartenol $C_{30}H_{50}O_2$	164; +41 (chlorofrom)	Balsamorhiza sagittata (Push.) Nutt. (Asteraceae)	46
65. 16S-Hydroxycycloartenol $C_{30}H_{50}O_2$	92; +21 (chloroform)	Balsamorhiza sagittata (Push.) Nutt. (Asteraceae)	46
66. Cycloart-24-ene-3β,26-diol $C_{30}H_{50}O_2$	154—155; +51 (chloroform)	Mangifera indica L. (Anacardiaceae)	50
67. 16S,22R-Dihydroxycyloartenol $C_{30}H_{50}O_3$	219 —	Balsamorhiza sagittata (Push.) Nutt. (Asteraceae)	46
68. Genin of quadranguloside $C_{30}H_{50}O_3$	170; +43 (methanol)	Passiflora quadrangularis L. (Passifloraceae)	51
69. Cycloart-25-ene-3β-24,27-triol $C_{30}H_{50}O_3$ (24-epimers)	190—192; +18.8 (chloroform)	Mangifera indica L. (Anacardiaceae)	50
70. 22,25-Epoxy-9,19-cyclolanostane-3β,21,22R-triol $C_{30}H_{50}O_4$	184—185,5; +45 (methanol)	Passiflora quadrangularis L. (Passifloraceae)	52
71. 21,24R-Epoxy-9,19-cyclolanostane-3β,25,26-triol $C_{30}H_{50}O_4$	138—140; +17.8 (methanol)	Passiflora quadrangularis L. (Passifloraceae)	52
72. 20S,24R-Epoxycycloartane-3β,15α,16β,18,25-pentaol $C_{30}H_{50}O_6$	Amorphous —	Beesia calthaefolia Maxim. (Ranunculaceae)	53
73. Cycloartane-3β,24,25-triol $C_{30}H_{52}O_3$ (24 epimers)	154-156; 0 (chloroform)	Mangifera indica L. (Anacardiaceae)	50
74. Cyclofoetigenin A $C_{30}H_{52}O_4$	182—184; +68,2 (methanol)	Thalictrum foetidum L. (Ranunculaceae)	54
75. Cyclofoetigenin B $C_{30}H_{52}O_5$	240—242; +72 (methanol)	Thalictrum foetidum L. (Ranunculaceae)	55
76. 16β,23R:24S,25-Diepoxy-23-methoxycycloartan-3-one $C_{31}H_{48}O_4$	211—212; —	Viguiera dentata (Asteraceae)	43
77. Jessic acid $C_{31}H_{48}O_5$	196—202; +55,5 (pyridine)	Combretum elaeagnoides (Combretaceae)	56

TABLE 2. (continued)

1	2	3	4
78. Heynic acid $C_{31}H_{50}O_3$	235–237; +40 (chloroform)	Heynea trijuga Roxb. (Meliaceae)	57
79. Methyl jessate 1α,11α-oxide $C_{32}H_{48}O_5$	165–167; +66,8 (chlorofrom)	Combretum elaeagnoides (Combretaceae)	58
80. Methyl jessate $C_{32}H_{50}O_5$	220–223; +60,4 (pyridine)	Combretum elaeagnoides (Combretaceae)	56
81. 3-Epicycloaudenol $C_{31}H_{52}O$	140; −10 (chloroform)	Euphorbia caudicifolia (Euphorbiaceae)	59
82. 3-Acetoxycycloart-23-en-25-ol $C_{32}H_{52}O_3$	148–150; +43 (chloroform)	Sapium insigne Trimen (Euphorbiaceae)	60, 61
83. Genin of beesioside III $C_{32}H_{52}O_7$	— +21,7 (methanol)	Beesia calthaefolia (Maxim.) Ulber. (Ranunculaceae), Souliea vaginata (Maxim.) Franch. (Ranunculaceae).	62
84. Genin of beesioside II $C_{34}H_{54}O_4$	Amorphous +28,7 (methanol)	Beesia calthaefolia (Maxim.) Ulber. (Ranunculaceae)	53
85. Mollic acid 3-O-α-L-arabinoside $C_{35}H_{56}O_8$	—	Combretum molle (Combretaceae)	63
86. Mollic acid 3-O-β-D-xyloside $C_{35}H_{56}O_8$	235–237; +39,5 (pyridine)	Combretum molle (Combretaceae)	47
87. Jessic 3-O-α-L-arabinopyranoside $C_{36}H_{56}O_9$	225–227; +52,6 (pyridine)	Combretum elaeagnoides (Combretaceae)	56
88. Beesioside III $C_{37}H_{60}O_{11} \cdot 0.5H_2O$	178–182: 220 solidifies; 247–249; +9,2 (methanol)	Beesia calthaefolia (Maxim.) Ulber. (Ranunculaceae), Souliea vaginata (Maxim.) Franch. (Ranunculaceae)	88
89. Beesioside II $C_{39}H_{62}O_{12} \cdot 0.5H_2O$	149–151; +9,3 (methanol)	Beesia calthaefolia (Maxim.) Ulber. (Ranunculaceae)	53
90. 24-Methylenecycloartanyl p-hydroxycinnamate $C_{40}H_{58}O_3$	255; +28,3 (chloroform)	Cirrhopetalum elatum (Orchidaceae)	64
91. 22,25-Epoxy-9,19-cyclolanostane-3-β,21,22R-triol-3-O-β-gentiobioside $C_{42}H_{70}O_{14}$	167–168; +6 (methanol)	Passiflora quadrangularis L. (Passifloraceae)	52
92. 21,24R-Epoxy-9,19-cyclolanostane-3β,25,26-triol-3-O-β-gentiobioside $C_{42}H_{70}O_{14}$	189–191; +5 (methanol)	Passiflora quadrangularis L. (Passifloraceae)	52
93. Cyclofoetoside A $C_{47}H_{80}O_{17}$	265–266; +22 (pyridine)	Thalictrum foetidum L. (Ranunculaceae)	65
94. Cyclofoetoside B $C_{47}H_{80}O_{18}$	194-197; +15,7 (pyridine)	Thalictrum foetidum L. (Ranunculaceae)	66
95. Quadranguloside $C_{54}H_{90}O_{23}$	164–165; −11 (methanol)	Passiflora quadragularis L. (Passifloraceae)	51
96. 24-Methylene-3,4-secocycloart-4(28)-en-3-oic acid $C_{31}H_{50}O_2$	—	Abies sibirica Ledeb. (Pinaceae)	67
97. Cyclopholidonol $C_{31}H_{52}O$	174–176; +41,1 (chloroform)	Pholidota chinensis Lindl. (Orchidaceae)	68
98. Roxburghiadiol A $C_{29}H_{48}O_2$		Aglaia roxburghiana (Meliaceae)	69
99. Roxburghiadiol B $C_{29}H_{48}O_2$		Aglaia roxburghiana (Meliaceae)	69
100. Cyclopholidone (cyclootochilone) $C_{30}H_{48}O$	148–150; +72,8 (chloroform) 140; +81,4 (chloroform)	Pholidota chinensis Lindl. (Orchidaceae), Otochilus porecta, Otochilus fusca (Orchidaceae)	68, 70

TABLE 3. Chemical Shifts and Stereochemistries of the C-20 and C-24 Atoms in the 20,24-Epoxycycloartanes

Compound	δ_{C-20}	δ_{C-24}	$\Delta\delta$ ($\delta_{C-20}-\delta_{C-24}$)	Configuration	Literature
3	87,0	81,7	5,3	20R, 24S	7
4	87,14	81,56	5,58	20R, 24S	14
5	87,1	81,6	5,5	20R, 24S	8,9
6	86,7	85,0	1,7	20S, 24R	8,9
72	86,2	85,2	1,0	20S, 24R	53
83	85,8	83,1	2,7	20ξ, 24ξ	62
84	84,4	83,5	0,9	20S, 24R	53
101*	84,6	83,1	1,5	20ξ, 24ξ	62

*(101) is the 3,16-diacetate of (83).

More than ten compounds or genin nature isolated from plants of the genus Astragalus and biogenetically interrelated are known. In this respect cycloorbigenin (2) must obviously be considered as an intermediate form on the evolutionary pathway to the appearance of the norcycloartane dasyanthogenin (1). The most widely distributed are cyclosieversigenin (5) and its glycosides.

Attention is attracted by the fact that no glycosides have been found of the 3-keto-compounds cycloasgenins A (3) and B (8) and 3-dehydrocycloasgenin C (7). This fact suggests that in Astragalus plants the cycloartanes are initially glycosylated at the C-3 hydroxy group. In favor of this hypothesis may also be the fact that the monodesmosidic glycosides of the plants under discussion that have been described consist of derivatives exclusively at the C-3 hydroxy group. At the same time, while monodesmosidic glycosides at C-3 of cyclosieversigenin (5), cycloasgenin C (9), cyclogalegigenin (6), cycloorbigenin (2), and dasyanthogenin (1) have been detected, no natural monodesmosides at other centers of glycosylation have been described from plants of the genus Astragalus. It must be assumed that the 3-ketocycloartanes (3, 7, and 8), isolated only from A. taschkendicus, are not substrates of the enzyme system of this plant responsible for glycosylation.

In various milk vetch species, two genins enantiomeric in the side chain have been isolated -- cyclosieversigenin (5), [2, 6-8] and cyclogalegigenin (6) [7-9]. Cycloastragenol [10] and astramenbrangenin [11, 12] isolated from A. membranaceus are identical with cyclosieversigenin.

The determination of the sterochemistry of the side chains of the cycloartanes having a 20,24-epoxy function proved to be no easy task. The unambiguous answer to this question in the early period became possible thanks to the x-ray structural analysis [8, 10, 12]. Subsequently, the presence of compounds with a known stereochemistry permitted the correct interpretation of the results of the chemical and spectral correlation of the structures of new substances. It was shown on the basis of chemical transformations and spectral characteristics that cyclosieversigenin (5) and cyclogalegigenin (6) have the alternative (20R,24S)- and (20S,24R)-stereochemistries. An x-ray structural investigation of cyclogalegigenin established its (20S,24R)-stereochemistry and, consequently, cyclosieversigenin has the (20R,24S)-configuration [8]. As was shown, cycloasgenin A (3) has a side chain identical with that of cyclosieversigenin [4].

Table 3 gives the values of the chemical shifts of the C-20 and C-24 chiral atoms of the known 20,24-epoxycycloartanes. As can be seen from the Table (compounds 3-6, 72), the chemical shifts of the C-24 atoms differ substantially according to their configuration, a 24R-atom resonating in a field approximately 3.5 ppm weaker than a 24S-atom. The signal of the 20R atom is likewise found in a weaker field than that of the 20S atom but the difference in this case is not so great (0.4 ppm). The magnitude of the difference in the chemical shifts ($\Delta\delta = \gamma_{C-20} - \delta_{C-24}$) is also characteristic for each enantiomer with respect to the side chain.

The presence and nature of substituents in the region of rings C and D are reflected in the values of the chemical shifts of the asymmetric atoms of the side chain that are under consideration. The acetylation of hydroxy groups at C-16 and C-18 leads to upfield shifts of the C-20 and C-24 signals by 1.8 and 1.7 ppm, respectively. The small deviations in the values of the C-20 and C-24 chemical shifts in compound (83) are obviously the

TABLE 4. Correlation of the Stereochemistry at C-24 with the Values of the Difference Dichroic Adsorption and the C-24 and H-24 Chemical Shifts in 16β,24,25-Triols

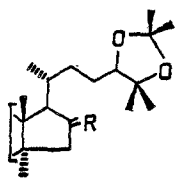
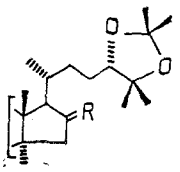
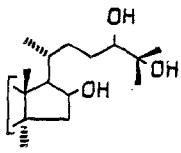
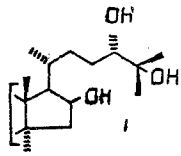
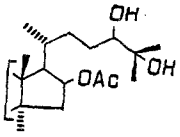
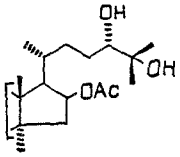
Configuration at 24 h	Compounds		$\delta_{H\text{-}24}$	Literature
R		102. R = 	3.20 q	6
		103. R = 	3,48 q	6
		104. R=O	3,59 q	6
S		105. R = 	3,80 q	54
		106. R = 	3,82 q	16
		107. R = 	3,85 q	55
		108. R = 	3,55 q	16
		109. R=O	3,67 m	54
		110. R=O	3,66 m	16
R		8	80,46	18
		9	80,52	18
S		74	77,2	54
		75	77,3	55
R		111	$\Delta\varepsilon$ (λ): −6,05 (320 nm)	6
S		112	+1,97 (325 nm)	55

TABLE 5. Chemical Shifts of Protons Geminal to Hydroxy Groups and Acetoxy Groups Located in the Polycyclic Part of the Cycloartane Molecule

Proton	Compound, literature	Chemical shifts, multiplicities, and SSCCs the gem-hydroxylic protons		Compound, literature	Chemical shifts, multiplicities, and SSCCs the gem-hydroxylic protons	
		δ, ppm	J, Hz		δ, ppm	J, Hz
1β	77 [56]	[3,37 t]	$W_{1/2}$=7	113 [71]	(4,75 t)	(3)
	81 [56]	3,58 t	$W_{1/2}$=6			
3α	6 [9]	3,24 dd	11,2; 4,8	116 [9]	[4,5 m]	
		[3,55 dd]	[11,2; 4,8]			
	114 [72]	[4,30 dd]	[11,0; 5,2]			
	77 [56]	[5,0 m]		113 [71]	(5.96 dd)	(12; 5)
	81 [56]	4,52 dd	11; 5			
	75 [55]	[3,34 dd]*	$\sum$ J = 16,2			
6β	6 [9]	3,48 ddd	9,8; 9,8; 3,8	116 [9]	[4,6 m]	
		[3,69 ddd]	[9,6; 9,6; 3,6]			
	117 [2]	4,12 ddd	10,5; 10,5; 4,0	118 [2]	[5,48 ddd]	[10,5; 10,5; 4,0]
		[4,34 ddd]	[10,5; 10,5; 4,0]	119 [13]	[4,80 ddd]	[10; 10; 3]
7α	2 [13]	[3,70 ddd]	[10; 10; 3]			
11β	122 [73]	3,81 m*	$W_{1/2}$ = 15			
	3 [4]	[4,19 dd]	[9,9; 2,5]	123 [4]	[5,13 dd]	[6,8; 2,0]
	8 [18]	[4,38 dd]*	[9,3; 3,4]	125 [18]	5,11 dd*	6,8; 2,3
12α	84 [62]	3,68 dd*	8,1; 5,7	126 [74]	4,87 dd*	
				127 [75]	4,88 dd*	
15β	122 [73]	3,64 m*				
	72 [53]	4,03 br.s*		84 [62]	4,52 d*	3,2
	120 [76]	[4,40 s]*		121 [70]	5,12 s*	
16α	6 [9]	[4,70 ddd]	[$\sum$ J = 21]	116 [9]	[5,37 m]	
		[4,87 ddd]*	[$\sum$ J = 21]			
		4,54 ddd	$\sum$ J = 21			
	3 [4]	[4,90 ddd]	[7,3; 7,3; 7,3]	124 [4]	[5,44 m]	
		[5,03 ddd]*	[7,3; 7,3; 7,3]			
	117 [10]	[4,99 m]*				
	8 [18]	[4,75 ddd]*	[$\sum$ J = 20,2]	125 [18]	5,32 ddd	$\sum$ J = 21
	75 [55]	[4,74 ddd]*	[$\sum$ J = 20,4]			
	74 [54]	[4,78 ddd]*	[7,9; 7,5; 4,6]			
	114 [72]	[4,85 ddd]*	[4,8; 7,9; 8,4]	115 [72]	[5,59 ddd]*	8,0; 8,0; 4,4
2H-18	72 [53]	4,24 s*		85 [53]	4,29; 4,79 d*	12,2
2H-29	114 [72]	[3,78; 4,22 d]*	10,5	115 [72]	[3,80; 4,20 d]*	11,4
2H-30	75 [55]	[3,52; 4,37]*	11,3			

Note. The indices given in curved brackets were obtained with the use of deuterobenzene as solvent, those with square brackets with deuteropyridine, and the others with deuterochloroform, in the presence of HMDS as internal standard. The chemical shifts marked with an asterisk were measured relative to TMS.

consequence of the influence of the C-12β hydroxy group and the C-15α acetoxy group. On passing from (83) to its acetate (101), the C-20 and C-24 chemical shifts agree well with those of (84). On the basis of this fact and also of biogenetic considerations, it may be assumed that compound (83) has the (20S,24R)-stereochemistry.

In the selection of the alternative (20R,24S)- and (20S,24R)-stereochemistries, use may also be made of PMR spectra. In the PMR spectra of cyclosieversigenin and cycloasgenin A, which have the (20R,24S)-stereochemistry, a signal from one of the C-22 protons is observed in the 2.97-3.0 ppm region (C_5D_5N, HMDS) in the form of a quartet with broadened lines. In the spectrum of (20S,24R)-epoxycycloartane – cyclogalegigenin – however, the H-22 signal is present in a stronger field and is hidden in the methylene "hump." The corresponding signal in the spectrum of quisquagenin (4) is found at 2.57 ppm ($CDCl_3$, TMS) [14].

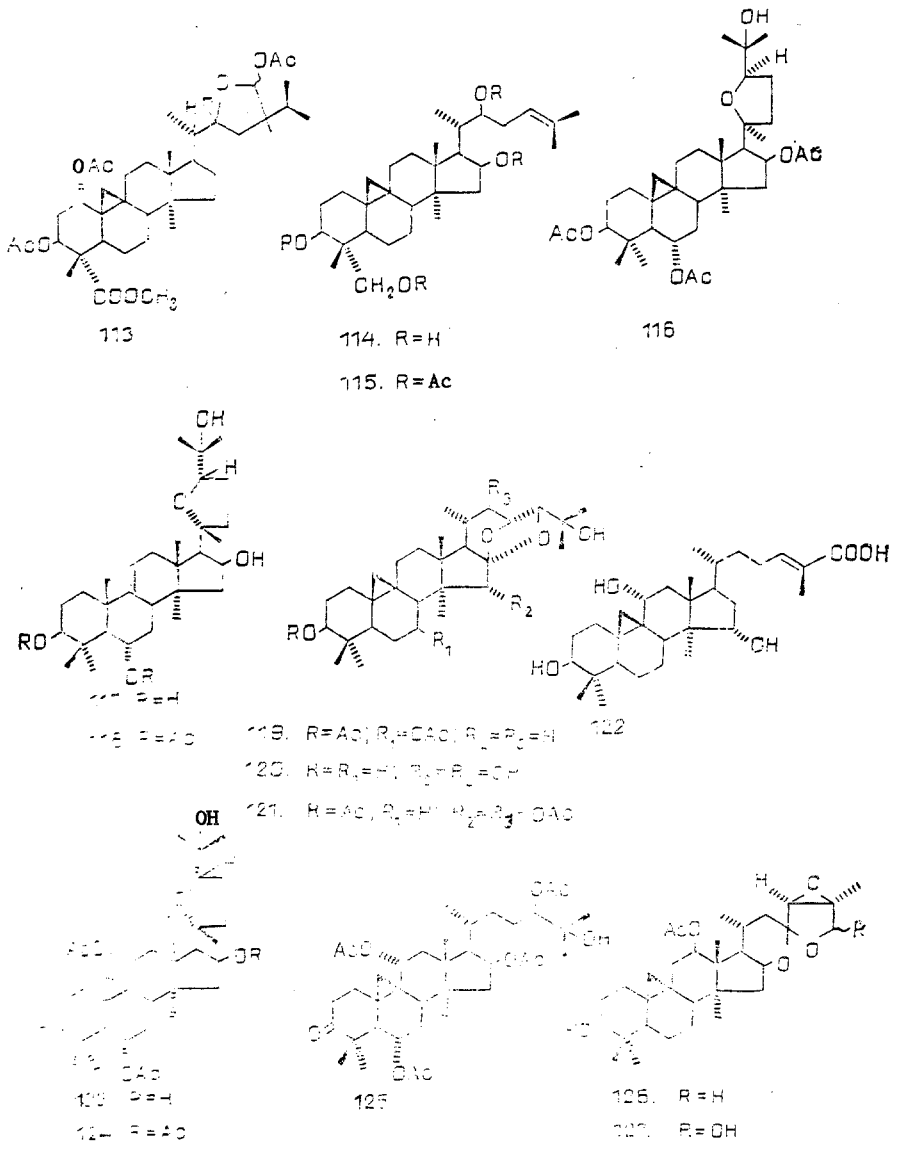
Proof of the C-24 stereochemistry in compounds having an acyclic side chain and a 24,25-diol grouping merits attention. The capacity for forming adducts with complex-forming

reagents which reveal Cotton effects on the circular dichroism (CD) curves is used for determining the C-24 stereochemistry [6, 55]. A negative sign of the effect indicates the R-configuration and a positive sign the S-configuration of the chiral center under consideration (Table 4). Conclusions concerning the C-24 configuration made on the basis of measurements of CD curves have permitted a correlation to be drawn between the chemical shifts of the carbon atom under discussion and its configuration.

In the ^{13}C NMR spectra of the 16β,24,25-triols, the signal of a 24R-carbon atom is shifted downfield by 3.2-3.3 ppm in comparison with that of a 24S-atom.

An interesting correlation can also be traced between the chemical shift of the H-24 atom and the C-24 configuration in the PMR spectra of 24,25-isopropylidene derivatives of the 16β,24,25-triols. The signal of the proton at a 24R-carbon atom is shifted downfield by 0.6 ppm in comparison with the signal of a proton attached to a carbon atom in the same position but with the opposite stereochemistry. As follows from Table 4, the magnitude under consideration also depends on the nature of the substituent at C-16. On the acetylation or oxidation of a secondary 16β-hydroxyl, the values of the H-24 chemical shifts of the two isomers approach one another and the difference between them reduces to a minimum, although in the case of the R-configuration, the signal of the H-24 proton remains the high-field signal in each pair of isomers.

Table 5 gives the chemical shifts, multiplicities, and spin-spin coupling constants of the gem-hydroxylic and gem-acetoxylic protons located in the polycyclic part of the molecules of the cycloartanes.



A hydroxy group at C-1 in the known cycloartanes has the α-orientation. No compounds with hydroxy functions at C-2 have been described. A hydroxyl at C-3 is β-oriented in the overwhelming majority of cases, and the chemical shift of the geminal protein depends on the substituents at C-29 and C-30. The presence of a hydroxy group at C-29 (114) or of a 4α-carboxy group (77, 80) leads to an appreciable downfield shift of the 3α-H signal in comparison with that of the cycloartane (6) not substituted in the positions under consideration. The presence of a hydroxyl at C-30 (75) is reflected in a slight upfield displacement of the 3α-H chemical shift.

Compounds with 6α-hydroxy group have been isolated from plants of the genus Astragalus. The proton geminal to a 6α-OH group experiences the screening effect of the cyclopropane ring and, as a consequence of this in PMR spectra its signal is found in a considerably higher field that the corresponding signal in the spectrum of lanostene (117).

The influence of a 6α-hydroxyl on the chemical shift of the signal of a 4α-methyl group in the PMR spectra when pyridine is used as solvent is characteristic. A pronounced downfield shift of the 4α-CH_3 signal to 1.8 ppm is observed [2, 4, 6, 9, 16-18]. This takes place thanks to the spatial propinquity of the 6α-OH and 4α-CH_3 groups, because of which a descreening action of the pyridine is shown.

A similar action of pyridine on the chemical shifts of the protons at C-15 [13] and on the cyclopropane protons [4, 18] is observed in the spectra of cycloartanes having 7β- and 11α-hydroxy groups, respectively.

The protons at C-15 in the spectrum of cycloorbigenin 3,7-diacetate (119) resonate at 1.91 and 2.26 ppm. In the spectrum of cycloorbigenin (2), the same signals are shifted downfield and are found at 2.46 and 2.70 ppm.

The resonance lines of the cyclopropane protons in the spectra of the cycloartanes (3) and (8) are located at 0.5 and 1.6 ppm. At the same time, in compounds having no 11α-OH group the signals under consideration are located between 0.2 and 0.5 ppm.

Unlike a hydroxyl at C-15 which may have either an α- or β-configuration, oxy functions at C-12 and C-16 usually possess the β-orientation. The value of the 16α-H chemical shift varies according to the structure of the side chain, the signal of the proton under consideration in the spectra of cycloartanes with aliphatic side chains being located in a higher field by 0.25-0.30 ppm.

While the protons of a hydroxymethyl group at C-18 resonate in the form of a singlet, the gem-hydroxylic protons at C-29 and C-30 appear as doublet interconnected in the manner of an AB system. Differences in the chemical shifts (Δδ) of the H-29 and H-29' protons (0.40-0.45 ppm) and the H-30 and H-30' protons (0.80-0.85 ppm) in the spectra of compounds having a free hydroxy group in the position under discussion are diagnostic magnitudes.

The C-29 atom has the equatorial and the C-30 atom the axial orientation. In view of this, hydroxymethyl groups at C-29 and C-30 are readily distinguished by the chemical shifts of the corresponding carbon atoms. The C-29 atom resonates at 68-72 ppm, and the C-30 atom at 64-65 ppm [55, 77].

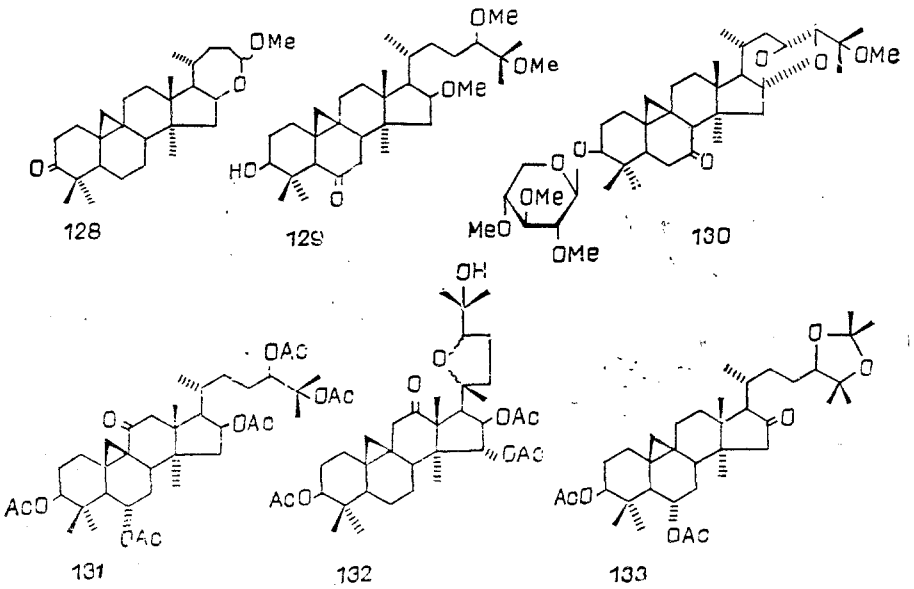
TABLE 6. Extrema on the Circular Dichroism Curves of Cycloartane Ketones [Δε(λ)]

Position of the keto function	Compound	Cotton effects of the keto functions	Literature
C-3	123	−1,39 (296 nm)	78
C-3	3	+1,44 (287 nm); −0,1 (320 nm)	4,78
C-6	129	+0,54 (310 nm)	78
C-7	130	−1,24 (305 nm)	*
C-11	131	+0,32 (297 nm)	78
C-12	132	−2,86 (288 nm)	62
C-16	133	−5,09 (305 nm)	6

*Not published.

Characteristic features of the circular dichroism (CD) curves and of the mass-spectrometric fragmentation of the cycloartanes have been found.

An influence of a 6α-hydroxy group on the nature of the Cotton effect due to a 3-keto function has been established which consists in its splitting into two components: negative in the 315-322 nm region and positive at 280-290 nm [78]. This fact was used in proving the structures of the 6α-hydroxy-3-ketocycloartanes [17, 18]. Table 6 gives the extrema on the circular dichroism (CD) curves of cycloartane ketones.



The mass spectra of cycloartanes having no oxygen functions in ring B are characterized by the peaks of the ion formed as the result of the splitting out of ring A [1]. The formation of this ion depends on the presence of oxy and keto functions in rings B and C (at C-11). The presence of a hydroxy or a carbonyl group at C-6 or C-7 leads to the disappearance of the ion under consideration. In the mass spectra of compounds having hydroxy groups at C-6 and C-11 simultaneously the peak of this ion reappears.

In view of the fact that, in an acid medium, cycloartanes isomerize to lanost-9(11)-enes, the production of the native genin from glycosides is the most important step in structural studies. Hydroxy groups at C-29 and C-30 or a carboxy function including the C-29 carbon atom promote isomerization, apparently by a mechanism of intramolecular catalysis. As a consequence of this, it is impossible to obtain a native genin with analogous functions by transformations including a stage of acid hydrolysis [55, 72, 77, 79]. Some points connected with the migration of the cyclopropane ring have been considered in [1].

Intramolecular catalysis also takes place on the hydrolysis of cycloorbicoside G (19), thanks to which the D-glucopyranose residue attached to the tertiary hydroxy group is eliminated more readily than the D-xylopyranose residue present at the secondary hydroxyl [28]. This is shown by the formation, as the only progenin, of cycloorbicoside A (12), containing a D-xylose residue. In this case, the oxygen atom of the ketal system assumes the role of catalyzing function.

The possibility of using acetylation for resolving questions traditionally answered by methylation has been shown [20].

Plants producing cycloartanes are widely used in traditional medicine. The active principle of the majority of these plants has been revealed as the result of investigations recently performed.

An extract from bugbane (Cimicifuga) rhizomes exhibits an effect in the prophylaxis of liver disorders caused by carbon tetrachloride [80]. Biochemical and histological investigations have shown that one of the components of bugbane rhizomes — cimigenol xyloside — is also effective in the prophylaxis of liver disturbances.

The preparation tsimitsilen obtained from the rhizomes with roots of Dahurian bugbane [Cimicifuga dahurica (Turcz.) Maxim] and consisting of the sum of the cycloartane glycosides possesses a hypolipidemic activity [81]. The hypocholesteremic effect of tsimitsilen is superior to that of the well-known drug polistonin.

Among the species of plants of the genus Astragalus that have been studied, the most widely distributed cycloartane is cyclosieversioside F (20 astragaloside IV, astramembranin I, astrasieversianin XIV) and its various derivatives. This also explains the extremely large number of studies devoted to various aspects of the pharmacological action of this glycoside.

An unpurified extract from Astragalus sieversianus Pall. possesses a diuretic and hypotensive action and can prevent the appearance of experimental gastric ulcer [82].

Cyclosieversioside D (27, a monoacetyl derivative of cyclosieversioside F) and a number of other derivatives of cyclosieversioside F possess an antiviral and antitumoral activity and a low toxicity on peroral or parenteral administration. The same glycosides are inductors of interferon [83]. Formulations or preparations for the treatment of hepatitis, herpes, and cancer are given in a patent [83].

Cyclosieversioside F possesses a hypotensive and antiinflammatory effect [84] and an analgesic and sedative activity [85]. This cycloside accelerates the protein metabolism in serum and the liver [86] and exhibits an immunostimulating effect [87]. To complete the picture, we may mention that cyclosieversioside F and other glycosides from Astragalus membranceus Bunge also exhibit cardiotonic activity [88].

24-Methylenecycloartenol stimulates ovulation in women [89].

A number of other pharmacological properties of the cycloartanes is given in [1].

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