Highly oxygenated guaianolides from some compositae plants

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The isolation of twenty new highly oxygenated guaianolides along with several known guaianolides from *Vernonia arkansana* (aerial parts and roots), *Pseudostiffia kingii* (aerial parts), *Dicoma anomala* (roots), *Hypochoeris cretensis*, *Saussurea salicifolia*, *S. involucrata*, *S. candicans*, *Bishopanthus soliceps* and *Blainvillea latifolia* (aerial parts) have been reviewed.

The sesquiterpene lactones are characteristic secondary metabolites of Compositae and their biological activities also make them of interest to pharmacologists. These lactones are formed by intramolecular cyclization of γ - or δ -hydroxy acids and broadly termed as cyclic esters. The suffix 'olide' in their names refers to the lactone moiety in the molecule. The α,β -unsaturated- γ -lactones are *cis*- or *trans*-fused to the C₆-C₇ or C₈-C₇ positions of the carbocyclic skeleton. The structural variation of the basic sesquiterpene skeleton involves the incorporation of an epoxy ring, hydroxy groups, ester moieties and reduction or oxidation of certain groups or even opening of the rings. Acids generally involve in esterification are 4 and/or 5 carbon acids, viz. methacrylic, angelic, tiglic, senecioic, methylbutyric acids or their hydroxy and/or acetoxy derivatives. Guaianolides are derived from guaiane skeleton. In this short review, we present the results of structure elucidation of two guaianolides from *Vernonia arkansana*¹, the senecioate and the hydroxysenecioate guaianolides from *Pseudostiffia kingii*², a 9 α -hydroxyguaianolide from *Dicoma anomala* sub sp. *cirsioides*³, a guaian-5,12-olide along with its precursor from *Hypochoeris cretensis*⁴, four 11 α -13-dihydro derivatives from *Saussurea salicifolia*⁵ L., an 8 α -propionyloxydehydrocostus lactone from *S. involucrata*⁵, three chlorojanerin derivatives from *S. candicans*⁶, five highly oxygenated guaianolides from *Bishopanthus soliceps*⁷ and a pumilin derivative from *Blainvillea latifolia*⁸.

Vernonia arkansana DC. has been investigated earlier^{9,10}. The re-investigation of roots afforded the known guaianolides 1-6¹¹ along with a new one 7. The structure of 7 was clearly arrived from the ¹H NMR spectral data which were similar to that of dehydrozalanin C 5. The stereochemistry of C-8 was deduced from couplings observed for H-8 and from the typical downfield shift of H-13' proton. Its molecular formula C₁₅H₁₆O₄ was established from high resolution mass spectrometry and identified as 8 α -hydroxydehydrozalanin C. The aerial parts on chemical

examination gave marginatin, three bourbonenolides and a new methoxyguaianolide 8. Its ¹H NMR data agree with its structure. From the signals of H-13, the presence of a methylene lactone was confirmed. However, the absence of signals for H-6, H-7 indicated a 6,7-double bond, its presence being supported by a downfield shifted doublet at δ 2.86, which was coupled with a broadened doublet at δ 2.26. These signals probably were those of H-1 and H-5. A methoxy group was present at C-10 and an acetoxy group at C-8 position. The stereochemistry at C-4 and C-10 was assigned by analogy to that of bourbonenolides and characterized as 8 α -acetoxy-4 β -hydroxy-10 α -methoxyguaian-6,7,11(13)-diene-6,12-olide. Probably lactone could be formed by fragmentation of bourbonenolide 9 by attack of methanol at C-10 as shown in Scheme 1. The bourbonenolide 9 has simultaneously been isolated from this plant.

Scheme 1

Pseudostiffia is a monotypic genus and belongs to the subtribe Pseudostiffinae¹². Earlier work on *Pseudostiffia kingii* H. Robins led to the isolation of acetylenes and triterpenes¹³. The re-investigation of its aerial parts reported the isolation of known guaianolides, viz. desacylcynaropicrin **10**¹⁴, arguerin B **11**¹⁵, cynaropicrin **12**¹⁶, 8 α -hydroxydehydrozaluzanin C **7**¹, the corresponding 11 β ,13-dihydroderivative **6**¹, as well as two further lactones, the senecioate **13** and the hydroxysenecioate **15**.

The structure of **13** was established from ¹H NMR data. Its NMR clearly showed the presence of a zaluzanin C derivative, as most signals were similar to those of zaluzanin C. However, an additional seneciyoxy residue was present. Spin decoupling showed that this group had to be placed at C-8 while from the coupling constants the α -orientation could be established. Acetylation afforded the acetate **14** and **13** was identified as 8 α -seneciyoxydehydrozaluzanin C. The ¹H NMR spectral data of **15** indicated that a hy-

droxylated ester group was present. Since the signal of the olefinic methyl group was at δ 2.15, the stereochemistry was also clear. All other signals were similar to those of **13**. Acetylation gave the diacetate **16** and its ¹H NMR spectrum further established the structure. **15** was named as 8 α -(4'-hydroxyseneciyoxy)dehydrozaluzanin C.

So far the results of chemical investigation of *Dicoma* species indicated the presence of characteristic oxygenated germacranolides^{17,18}. A re-investigation of the roots of *Dicoma anomala* Sond. subsp. *cirsiodes* (Harv.) Willd. afforded in addition to stigmasterol, sitosterol, lupenone, eudesmanolides, a known guaianolide (dehydrozaluzanin C) **5** and a new guaianolide **17**.

The ¹H NMR spectrum of **17** was very similar to **5**. The presence of a 9 α -hydroxy group was deduced from the downfield shifts of H-14 (5.09 s, 4.67 d) and H-9 (4.63 ddd) and the value of coupling $J_{8,9}$. This was confirmed by spin decoupling which allowed the assignment of all signals. The corresponding 9-O-angelate was isolated from *Zinnia* species¹⁹ and as expected the couplings $J_{8,9}$ were nearly the same. It was characterized as 9 α -hydroxydehydrozaluzanin C.

Earlier work on the genus *Hypochoeris* has shown that guaianolides related to lactucin may be characteristic for this genus²⁰⁻²². The chemical examination of the aerial parts of *Hypochoeris cretensis* Benth. showed the presence of taraxasterol, lupeol and its acetate, phytol, isoalantolactone and a new guaian-5,12-olide **18** and the corresponding precursor **19**.

The structure of **18**, which on addition of diazomethane afforded the pyrazoline **20**, was derived from the molecular formula and the high field ¹H NMR spectrum.

The presence of a methylene lactone followed from the typical pair of downfield signals at δ 6.62 and 5.71. The IR band at 1740 cm⁻¹ indicated a δ -lactone. The chemical shifts of two olefinic methyls and a quartet at δ 6.18 showed that most likely a guaianolide with a keto group at C-2 and a 1(10) as well as a 3,4-double bonds were present. The absence of a H-5 signal and the results of spin decoupling clearly showed that a 5,12-guaianolide was present, which

required an equatorial orientation of H-7. Accordingly, this signal was narrowly split only as all couplings were small. Inspection of a model further showed that the angles H-7-H-13 supported the observed small couplings of H-13. The stereochemistry of the pyrazoline derivative **20** was deduced from the observed downfield shift of H-6 β . The ¹H NMR spectral data of **19** showed that a methyl ester was present. The conformation was clearly different from that of **18** since H-7 was now axial as followed from the couplings observed. Spin decoupling allowed the assignment of all signals. Guaian-5,12-olide **18** was named as hypocretenolide and its precursor **19** as methyl hypocretenoate.

The large genus *Saussurea* (Compositae, tribe-cynareae) with more than 300 species²³ has been investigated chemically for acetylenes²⁴ as well as for sesquiterpene lactones. So far lactones are reported from nine species²⁵⁻³². Guaianolides related to cynaropicrin **12** are characteristic of this genus. Some other types of lactones were also reported from *S. lappa*²⁶. Three species, namely, *S. salicifolia*, *S. involucrata* and *S. candicans* have been examined. The aerial parts of *S. salicifolia* (L.) DC. gave arctigenin, matairesinol, trachelogenin, cynaropicrin **12**, 19-desoxyjanerin **21**, janerin **22**, desacyl-janerin-*O*-hydroxytiglate **23**, desacyljanerin **24** and 11 α ,13-dihydro derivatives **25-28**.

The polarity of lactones **25-28** was very similar, hence their separation was difficult. These could only be separated by TLC and HPLC.

The structures of **25** and **27** were followed from the ¹H NMR spectra which indicated that these compounds only differed in the nature of the ester groups. The typical exomethylene signals in the spectrum of cynaropicrin were replaced by a methyl doublet at δ 1.13 and a doublet quartet

at δ 2.77. Accordingly, these lactones were 11,13-dihydro derivatives of cynaropicrin and of the corresponding 4-hydroxytiglate. The configuration at C-11 was followed from the coupling $J_{7,11}$ (7 Hz), while a very similar compound with a 11 α -methyl showed as usual a large coupling²⁵. The ¹H NMR spectral data of **26** and **28** were similar to that of janerin, the 4 β ,15-epoxide of cynaropicrin³³ and with that of the corresponding 4-hydroxytiglate³⁴, respectively. However, again the signals of the exomethylene group (H-13) were replaced by a methyl doublet at δ 1.14 and a doublet quartet at 2.74. Subsequently, these lactones were 11,13-dihydro derivatives of the previously isolated methylene lactones. Again the coupling $J_{7,11}$ exhibited the presence of 11 β -methyl groups. The lactones **26** and **28** were identified as 11 α ,13-dihydrojanerin and 11 α ,13-dihydrodesacyljanerin-4-hydroxytiglate, respectively.

centaurepentin 35, repdiolide triol 36 in addition to tetrol 37, its 15-methoxy 38 and 15-acetoxy 39 derivatives.

The polarity of lactones 37-39 was very high and therefore their separation could be achieved by repeated preparative TLC and HPLC. The structure of 37 was established

R

	36	37	38	39
R ¹	H	H	Me	Ac
R ²	H	H	H	H
R ³	H	H	H	H
R ⁴				

Saussurea involucrata (Kar. et kir.) Sch. Bip. is used in the folk medicine by Mangolians and it is said to have activities similar to Ginseng. On examination it afforded costic acid, dehydrocostus lactone 2, its 11 β ,13-dihydro derivative 29, 8 α -hydroxydehydrocostus lactone 30, its acetate 31 and the corresponding propionate 32 as new guaianolide.

The structure of propionate 32 could be easily deduced from the ¹H NMR spectrum which was very close to that of the corresponding acetate³⁵ 31. The acetate signal of the latter was replaced by a triplet and a quartet at δ 1.17 and 2.41, respectively, and named as 8 α -propionyloxydehydrocostus lactone.

Previous work on *Saussurea candicans* C.B. Clarke led to the isolation of acetylenes²⁴. The aerial part of this plant on re-investigation gave arctigenin and matairesinol, cynaropicrin 12, desacylcynaropicrin 10, aguerin-B 11, janerin 22, 19-desoxychlorojanerin 33, chlorojanerin 34,

from ¹H NMR spectral data which revealed that this compound differed from repdiolide triol 36 in the nature of the ester moiety at C-8 position. Methyl acrylate signals were replaced by its 3-hydroxy derivative and subsequently methyl signal was replaced by a broad singlet at δ 4.39 inte-

grated for two protons. The chemical shifts of the other protons remained unaltered. A similar compound with a 4-hydroxytiglate ester function at C-8 was reported from *Centaurea imperialis*³⁶. On acetylation it gave two tetracetates **40** and **41**.

In the former case all the four hydroxyl groups acetylated and consequently H-3, H-15, H-19 were shifted downfield. In the latter case (**41**), 3-hydroxymethacrylate ester group hydrolyzed prior to acetylation and signals of methacrylate ester function (δ 6.33 s, 5.97 q, 4.39 s br) replaced by an acetate singlet at δ 2.19. The ^1H NMR spectral data of **38** and **39** were very similar to that of repdiolide triol **36** with additional peaks for a methoxy (δ 3.45) and an acetoxy (δ 2.18) functions, respectively. The H-15, H-15' doublets were shifted slightly upfield at δ 3.98 and 3.67 in former and shifted downfield at δ 5.03 and 4.22 in the latter case. Chemical shifts of the rest of protons of both the lactones remain unchanged. The lactones **37-39** were named as 15-deschloro-15-hydroxychlorojanerin, 15-deschloro-15-methoxychlorojanerin and 15-deschloro-15-acetoxychlorojanerin, respectively.

Bishopanthus soliceps is a member of a new monotypic genus of the tribe Liabeae of family Compositae³⁷. No work has been reported on this species. The aerial parts of *B. soliceps* afforded ferulic acid, the flavones pectolinarigenin, 3-desmethoxycentaureidin and eupatolitin, the guaianolides anhydrocumambrin A, 1-desoxy-1 α -peroxyrupicolin A and B, 11,13-dehydrocumatricarin as well as **42-46**.

The ^1H NMR spectral data showed **42** and **43** were hydroperoxides (s br 8.38, 8.47 respectively). A pair of doublets at δ 6.22 and 6.34 in the spectrum of **42** with a 6 Hz coupling clearly revealed that a guaianolide with a 2,3 --

double bond was present. Most signals were close to those of one of the epimeric endoperoxides isolated from *Tanacetum* species³⁸. However, these compounds had no 8-O-acetate group. When the shifts of H-5 and H-6 were compared with those of epimeric tanaparthin peroxides it was obvious that **42** was the 1 α ,4 α -isomer. Noe difference spectroscopy gave clear effects between H-14 and H-2 and H-9 α , between H-5 and H-7, between H-6 and H-8 and between H-15, and H-3 and H-5, which established the proposed configurations. Models indicated however, that the orientation of H-15 cannot be assigned from these results. As the configuration of the isomeric endoperoxides from the *Tanacetum* species was established, the configuration at C-4 in **42** was clear. The spectrum of **43** was in part similar to that of **42**. However, the olefinic signals were replaced by a pair of upfield shifted doublets which were due to epoxide protons. The β -orientation of the epoxide oxygen caused a downfield shift of the H-6 signal. Further, clear noe were observed between H-5 and H-7, between H-6 and H-8, between H-15 and H-3 as well as between H-14 and H-9 α and H-9 β . Inspection of models indicated that these effects required the proposed stereochemistry, while the couplings observed showed that the conformations of **42** and **43** were slightly different. Compound **42** was named as bishopantholide while **43** corresponding 2 β ,3 β -epoxybis-bishopantholide. The ^1H NMR spectra of **44** and **46** were again in part very similar. Both compounds were transformed by reduction with triphenylphosphine to the lactone **45** which was also present in the extract. The ^1H NMR spectrum of

45 differed from that of **42** by the presence of exomethylene proton signals. As the H-9 signals were shifted downfield, a 10 (14) – double bond was proposed. Compound **44** showed clear noe between H-6 and H-8, between H-15 and H-6 and H-3, between H-14 and H-2 and between H-14' and H-9 α . These results required the proposed configuration for **44-46** and the relative position of the hydroperoxide groups followed from the downfield shift of H-5 in the spectrum of **46** if compared with that of **44** and **45**. The lactone without an oxygen function at C-1 and C-4 was named bishopsolicepolide and consequently **44-46** were characterized as 1 α -peroxy-4 α -hydroxybishopsolicepolide, 1 α ,4 α -dihydroxybishopsolicepolide and 1 α -hydroxy-4 α -peroxy bishopsolicepolide, respectively.

So far two species of *Blainvillea* (Compositae, tribe-Heliantheae, subtribe-Ecliptinae) have been examined chemically and both gave melampolides and some other sesquiterpene lactones^{39,40}. The aerial parts of *Blainvillea latifolia* afforded zoapatanolides A and B, subacaulin **47** and a new guaianolide **48**.

The structure of **48** could easily be deduced from the ¹H NMR spectrum which was close to that of dehydroleucodin⁴¹ and in part to that of **47**⁴². The configuration at C-8 and C-9 followed from the observed couplings and the relative position of the ester group from the chemical shifts of H-8 and H-9. From spectral data it was characterized as 5-desoxyxypumilin.

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