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THE DITERPENOIDS OF TEUCRIUM SPECIES

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Abstract - This review describes the major advances reported during the last five years on the chemistry of these terpenoids.

The chemistry of the diterpenoids occurring in the genus Teucrium (family Labiatae) has shown a further remarkable development after the publication[1] in 1976 of a review dealing in part with this topic. Several new diterpenoids have been isolated by our group or by other researchers.

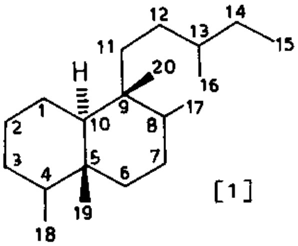
The present review aims at giving an up-to-date report on the structure and absolute stereochemistry of these products.

GENERAL FEATURES.

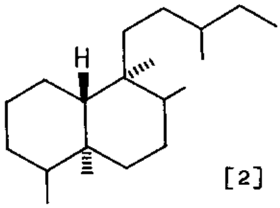
All the diterpenoids which have been isolated till now and whose structure has been elucidated, have the clerodane or 19-norclerodane skeleton (apart from the absolute configuration). All products have a furan ring, β-substituted with the remaining part of the terpene molecule. Additional heterocyclic features, occurring irregularly in the structures, are epoxide, γ-spirolactone, α,β-unsaturated γ-lactone, five-membered lactol, pyran rings; in one case, an α,β,β-trisubstituted furan ring occurs which involves carbon atoms 18, 4, 5, 6.

As for the absolute configuration, in our opinion there is a need for discussion about the nomenclature of the basic skeleton. The Rowe nomenclature[2] indicated [1] as clerodane and [2] as ent-clerodane. A recent proposal[3] by Rogers assigned to [1] and [2] the names ent-neo-clerodane and neo-clerodane. However, there is a risk of confusion in this new nomenclature since the neo-clerodanes [2] are related biogenetically to ent-labdanes in which C-20 is an α-substituent whilst the ent-neo-clerodanes [1] are related biogenetically to the normal labdanes in which C-20 is a β-substituent.

Therefore, we suggest to adopt the previous nomenclature again; in this paper, [1] will be indicated as clerodane and [2] as ent-clerodane.



[1]



[2]

All the diterpenoids from Teucrium species whose absolute stereostructure was determined, typically show ent-clerodane configuration [2]. However, the absolute configuration of several other products has not yet been investigated or surely determined.

These diterpenoids seem to be typical of the genus Teucrium and do not occur in other genera of Labiatae or in other families; the only exceptions are represented by teucvin and teucvidin each of which has been found in one species of the family Euphorbiaceae (see below).

PREVIOUS RESEARCHES.

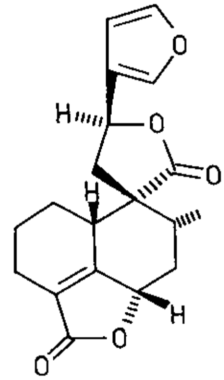
The first Teucrium diterpenoids whose structures were fully elucidated were teucvin^{4,5} [3] and teucvidin^{6,7} [4], isolated by Fujita from T.viscidum Blume var. miquelianum (Maxim.) Hara. Their absolute configurations rest on CD determinations and X-ray work.

Some years before, Brieskorn^{8} had extracted from T.polium L. three products, picropolin [5], 6-acetyl-picropolin [6] and the related hemiacetal isopicropolin [7], but their stereochemistry had not been ascertained.

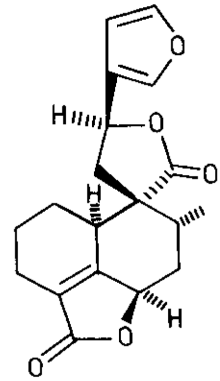
Subsequently, Popa and Reinbold isolated$^{9-13}$ seven substances from T.chamaedrys L.: teucrin A [8], teucrin B [9], teucrin C, teucrin D, teucrin E [10], teucrin F [11] and teucrin G [12]. Whereas the absolute configurations were given ^{12,13} for teucrin A, teucrin E and teucrin F, only relative stereostructures were assigned^{13} to teucrin B and teucrin G; no structural formulae were published for teucrin C and teucrin D.

In the meantime, teucvin [3] was extracted^{14,15} from T.cubense and also from Mallotus repandus (Euphorbiaceae)^{16}, and teucvidin was found^{17} in Croton caudatus Geisel (Euphorbiaceae).

Some of these products have a C_{20} clerodane skeleton (picropolin and its derivatives, teucrin B, teucrin E, teucrin F, teucrin G), whilst others have a C_{19} 19-norclerodane skeleton (teucvin, teucvidin, teucrin A).



[3]



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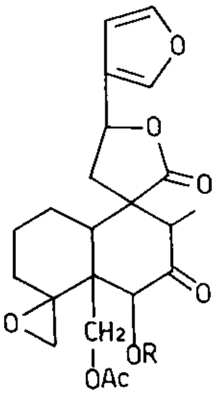
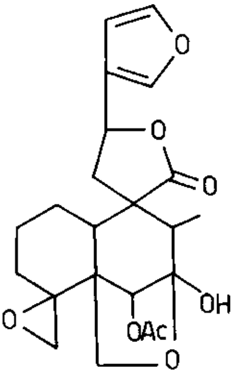


[5] R = H

[6] R = Ac



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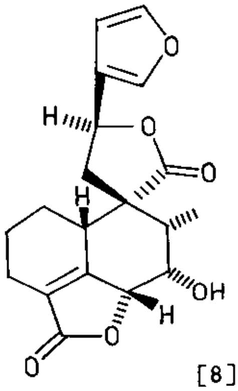
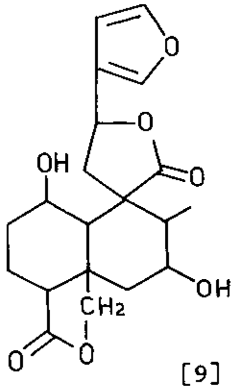
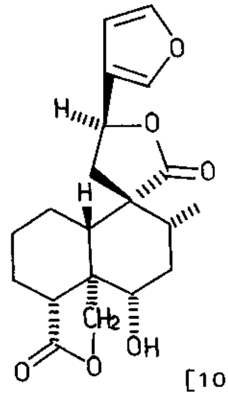


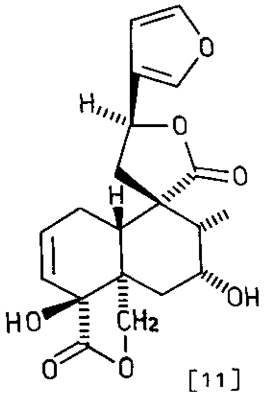
[8]



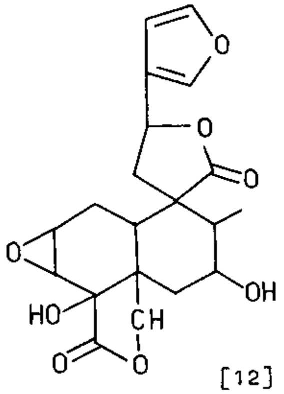
[9]



[10]



[11]



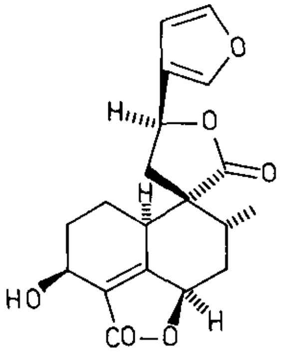
[12]

RECENT RESEARCHES.

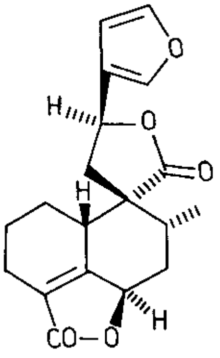
During 1977-1980 several *Teucrium* species were investigated by a joint group in Palermo (Piozzi and coworkers), Brighton (Hanson and coworkers) and Madrid (Rodriguez and coworkers).

T.flavum L. gave two new 19-norditerpenoids, teuflidin [13] and teuflin [14]. The first substance^{18} is 3β-hydroxy-teucvidin, and its structure was confirmed by X-ray analysis; the absolute configuration is proved by its negative CD curve due to the α,β-unsaturated γ-lactone and identical with the CD curve of teucvidin [4]. Teuflin^{19} is a more interesting product as it presents an unusual 10β-H/6α-H *trans* relationship: its stereochemistry relies on X-ray work and on the negative CD curve of the α,β-unsaturated γ-lactone.

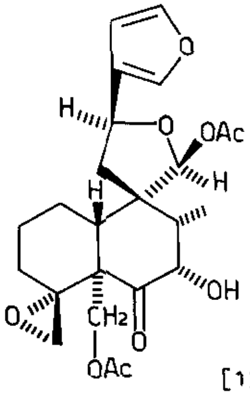
A new clerodane diterpenoid was found in *T.eriocephalum* Willk.: owing to the scarcity of product, the structure and the absolute configuration [15] of eriocephalin^{20} were determined mainly by spectroscopic methods and by X-ray diffraction; it has a positive CD curve associated with a C-6 ketone having ring B in a boat conformation, hence the *ent*-clerodane stereostructure is confirmed.



[13]

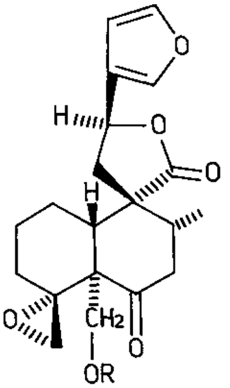


[14]



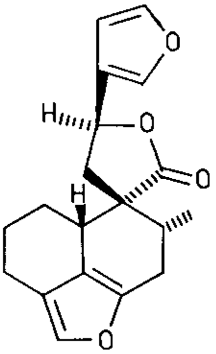
[15]

Extraction of *T.gnaphalodes* L'Hér. yielded four clerodanes. Gnaphalin [16] and 19-acetyl-gnaphalin [17] were easily interconverted; both products by mild alkaline treatment gave a 19-norclerodane furan [18] arising from a retroaldolic cleavage. This product was found to be identical with montanin-A, isolated from *T. montanum* L. (see below). As montanin-A had been oxidized to teucvin [3], also the absolute configuration of [16] and [17] was therefore ascertained^{21}. The *ent*-clerodane structure of [17] was eventually proved by X-ray diffraction^{22}. The easy loss of one carbon atom from [16] to [18] and the possibility of an oxidation to teucvin [3] gives an easy entry in the norclerodane series and suggests the hypothesis that a similar pathway can be responsible for the biogenetic transformation of ent-clerodanes into lactonic 19-nor-ent-clerodanes like teucvin and other products.



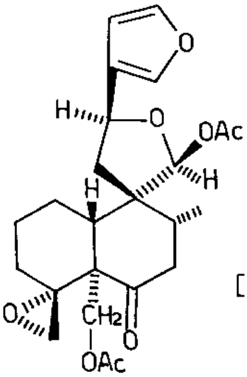
[16] R = H

[17] R = Ac



[18]

A third product, gnaphalidin [19], differs from 19-acetyl-gnaphalin only by the occurrence of a five-membered lactol ring instead of the γ-lactone system; gnaphalidin was correlated with 19-acetyl-gnaphalin, thus elucidating the absolute configuration[21]. The fourth substance extracted from T.gnaphalodes was proved to have structure [20] and absolute configuration corresponding to the ent-clerodane skeleton, as indicated by X-ray diffraction work[22]. The product seems to be identical with teucrin P_1 , occurring in T.polium L. (see below), apart from a discrepancy in the rotatory power value.



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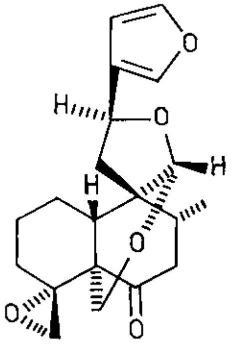
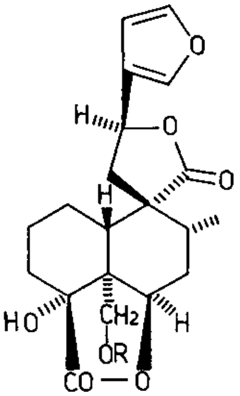


[20]

Another species, T.spinosum L., gave three diterpenoids[23]. One of them was easily identified with 19-acetyl-gnaphalin [17]; the other products, teuspinin and 19-acetyl-teuspinin, were assigned the structures [21] and [22]. Their ent-clerodane absolute configuration was proved quite recently[24] by X-ray work.



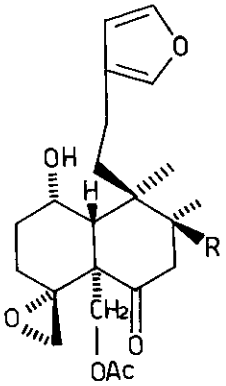
[21] R = H
[22] R = Ac

Significant features of the structure of teuspinin [21] are the tertiary equatorial hydroxy group on C-4 and the co-occurrence of the saturated γ-lactone ring C-18/C-6 with the groupment -CH$_2$OH on C-5: all these substituents are in axial orientation.

The diterpenes occurring in *T.fruticans* L. required a careful stereochemical investigation. Three products were isolated, all lacking the γ-spirolactone ring: for this feature, they are unique amongst *Teucrium* diterpenoids. The isomeric fruticolone [23] and isofruticolone [24] were correlated through the diketone [25] obtained by oxidation of both products[25]. The structure of 8β-hydroxy-fruticolone [26] was inferred on the basis of the close similarity of its NMR spectrum with that of fruticolone[26]. Although no direct correlation with known stereostructures had been performed, the negative CD curve of fruticolone [23] was consistent with an *ent*-clerodane with C-6 ketone having ring B in chair conformation. The CD curve of isofruticolone [24] having a C-1 ketone was recently[22] found to be negative, in agreement with that calculated for a 1-keto-5α-19-nor-steroid: hence isofruticolone and thus fruticolone must have the *ent*-clerodane stereochemistry.

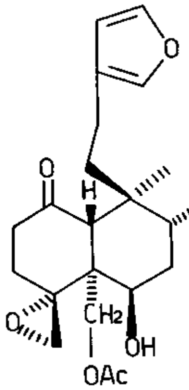
Other *Teucrium* species contain diterpenoids which occur in previously studied species and whose structures were already elucidated. So our group found eriocephalin [15] and 19-acetyl-gnaphalin [17] in *T.homotrichum* (= *T.carthaginense* Lange subsp. *homotrichum*)[27]; *T.intricatum* Lange[27] gave teucvin [3], and *T.scorodonia* L. subsp. *euganeum* (Vis.) Arcangeli[27] gave teuflin [14].

During recent years, several other groups were active in the field of *Teucrium* diterpenoids. So *T.montanum* L. was studied by Mollov and coworkers in Bulgaria. They isolated montanin-A [18] and montanin-B [27]: the latter was transformed



[23] R = H

[26] R = OH



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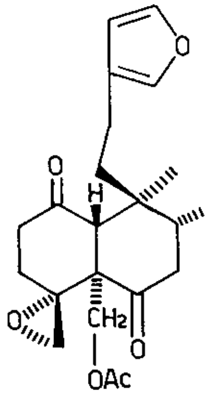
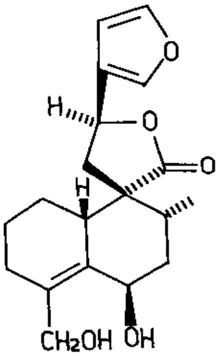
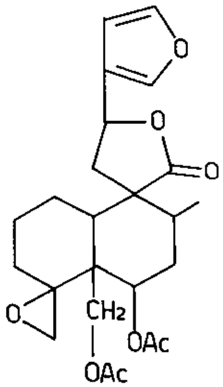


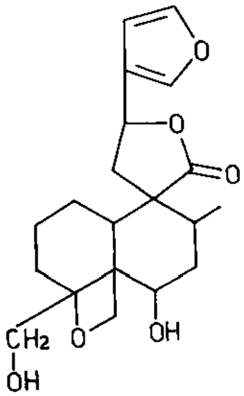
[25]



[27]



[28]

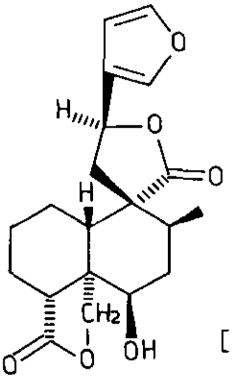


[29]

into the former and this one into teucvin [3], thus proving the absolute *ent*-clerodane stereostructure[28]. A third diterpene, montanin-C, was attributed[29] structure [28]: however, a product having structure [28] was synthesized by us[22] starting from 19-acetyl-gnaphalin [17] and by Mollov from teupolin-I and teupolin-II (see below) and found to be somewhat different; hence, the structure of montanin-C probably needs further investigation. Finally, montanin-D was reported[30] to have structure [29], with an unprecedented oxetane ring; no absolute stereochemistry was indicated for montanin-C and montanin-D. Also in this species two C_{19} and two C_{20} derivatives cooccur.

An Armenian-Hungarian group investigated *T.hyrcanicum* L., growing in Armenia: four diterpenes were isolated[31] and named teucrin H_1, teucrin H_2, teucrin H_3 and teucrin H_4. The first product was assigned[32] structure [13] and the same absolute configuration of teucvidin, on the basis of the negative CD curve: indeed, the substance is identical with teuflidin isolated by us from *T.flavum* (see before).

Teucrin H_2 is a C_{20} clerodane and has structure [30] (or its enantiomeric structure, as the absolute configuration was not ascertained)[32]; it has two saturated γ-lactone rings and the peculiarity of the unusual axial methyl group on C-8: in fact, all the other clerodanes from *Teucrium* species do have the equatorial methyl group on C-8.



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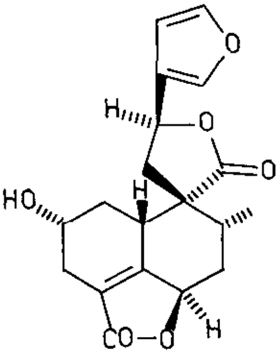


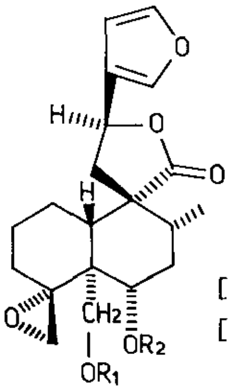
[31]

Teucrin H_3 is identical with 19-acetyl-gnaphalin [17]: the structure was determined independently and the absolute configuration was deduced from the negative CD curve[32].

Teucrin H_4 is a new C_{19} nor-clerodane with stereostructure [31] and the unusual 10β-H/6α-H *trans* relationship already observed by us in teuflin [14]; the Authors[32] left a doubt on the stereochemistry on C-12, but comparison with ^{1}H-NMR coupling constants of H-12 of teuflin allows us to conclude that there must be the usual 12α-H orientation. Hence teucrin H_4 is the 2α-hydroxy derivative of teuflin.

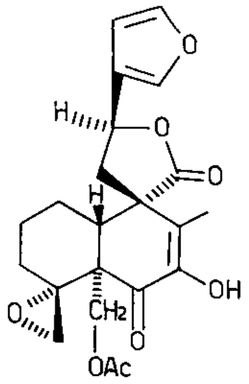
A peculiar problem is connected with T.polium L. No further work appeared on the stereochemistry of picropolin [5] and its derivatives [6] and [7]. However, Popa in Soviet Union investigated[33] a sample of T.polium collected in Moldavia: he found neither [5] nor [6] nor [7], but instead he isolated two new products named teucrin P_1 and teucrin P_2. No data or structural formula were given for the latter, whereas teucrin P_1 was attributed structure [20] apart from the undetermined absolute configuration. The same product was found by us to occur in T.gnaphalodes (see before) and independently proved to have the same structure and also the ent-clerodane stereochemistry.

Quite recently, two more papers appeared on T.polium. Mollov in Bulgaria isolated five diterpenes: 19-acetyl-gnaphalin [17], montanin-B [27], teucrin P_1 [20] and the novel teupolin-I [32] and teupolin-II [33]. The last two products were correlated mutually and with 19-acetyl-gnaphalin, and their stereostructures thus proved[34].



[32] R_1 = Ac R_2 = H

[33] R_1 = H R_2 = Ac



[34]

The second paper dealt with a sample of T.polium collected in Spain: Marquez and Valverde[35] isolated picropolin [5], 19-acetyl-gnaphalin [17] and a novel product, which was attributed diosphenol structure [34]. The last product was transformed into picropolin by $NaBH_4$ reduction; however, the Authors did not assign the absolute configuration to picropolin and to [34], although suggesting probable ent-clerodane stereostructure.

We must emphasize that T.polium is described[36] to exist in five subspecies: subsp. polium, subsp. aureum (Schreber) Arcangeli, subsp. capitatum (L.) Arcangeli, subsp. pii-fontii Palau, subsp. vincentinum (Rouy) D.Wood. Unfortunately, the samples studied by Brieskorn, Popa, Mollov and Marquez were collected in different countries (Germany, Moldavia, Bulgaria, Spain) and not identified botanically as the subspecies. From the chemical point of view, they seem to be quite different and need further investigation and classification.

With the purpose of making this point clear, our group quite recently undertook the investigation of two well identified samples of T.polium subsp. aureum, collected in Western Sicily and in Southern Spain. Surprisingly, we found still different products, even differing from one sample to the other.

In the case of the Sicilian sample of T.polium subsp. aureum no new diterpenoid was isolated; instead we extracted[27] some gnaphalidin [19] and large amounts of the product [20] believed to be teucrin P_1 and identical with that obtained from T.gnaphalodes.

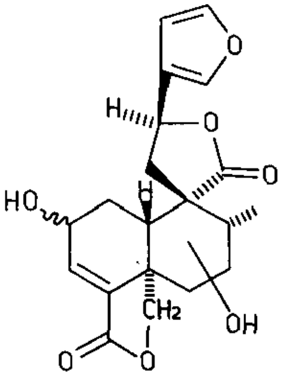
From the Spanish sample of T.polium subsp. aureum we isolated 19-acetyl-gnaphalin [17] and a new product, auropolin[27]; it has formula $C_{24}H_{30}O_9$ and includes two acetyl groups. Work is still in progress to elucidate its structure, as auropolin seems to have some features differing from Teucrium diterpenoids previously studied.

ADDENDUM.

Teuflin [14] has recently been isolated by Fujita[37] from T.viscidum subsp. miquelianum beside teucvin and teucvidin, and its structure has been confirmed.

The subspecies of T.polium investigated by Marquez and Valverde was identified as T.polium subsp. capitatum (L.) Arcangeli[38].

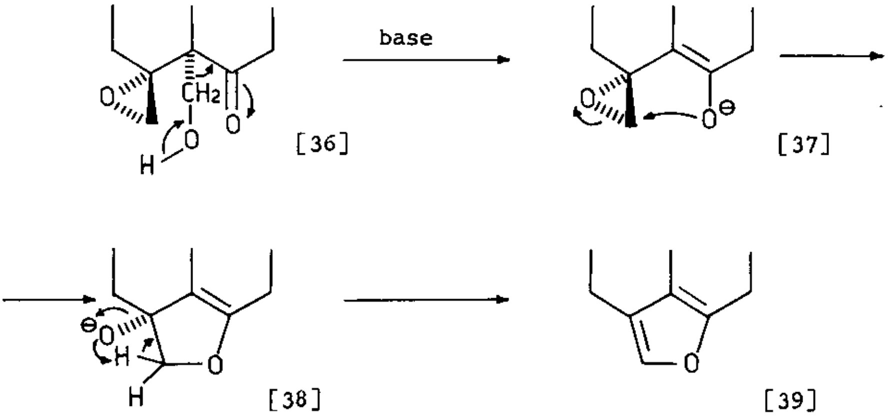
Investigation of T.fragile Boiss. was undertaken by our group: only a very small quantity of a new diterpenoid was isolated. This product, named teugin, is a C_{20} clerodane with the γ-spirolactone ring and a second γ-lactone system between C-18 and C-19; it has a $\Delta_{3,4}$ double bond with an allylic hydroxy group on C-2; another secondary hydroxyl occurs on C-6 or C-7. Work is in progress to elucidate the structure - tentatively draft as [35] - and the absolute configuration[27].



[35]

BIOGENESIS OF TEUCRIUM DITERPENOIDS.

No experimental work was done so far on the biogenesis of these products. On the basis of the well accepted theory, the *ent*-clerodane skeleton arises from *ent*-labdane, whereas the formation of the furan ring must occur at some undetermined steps of the biogenetical pathway. The elimination of C-19 transforms C_{20} into C_{19} diterpenes and may occur *in vivo* on structures like [36] by retroaldolic splitting of formaldehyde following the cyclization-dehydration pathway [36]-[37]-[38]-[39]. The base catalyzed transformation of gnaphalin [16] into montanin-A [18] observed *in vitro* may be considered as a biomimetic example of this reaction. A similar treatment was also performed on fruticolone [23] and gave the related furan.



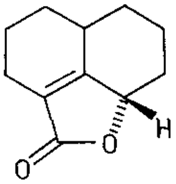
RESEARCH TECHNIQUES.

Whereas routine use of IR, MS and ^{1}H-NMR spectra is basic to any work on these products, the last few years have seen increasing application of other methods. So ^{13}C-NMR spectra are now currently used: data are available for almost all *Teucrium* diterpenoids.

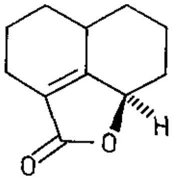
Owing to the complexity of these structures, a wide use of X-ray crystallography was made. Data were reported for teucvin, teucvidin, teuflin, teuflidin, 19-acetyl-gnaphalin, eriocephalin, fruticolone, teucrin P_1. In several cases (eriocephalin, teucvin, 19-acetyl-gnaphalin, teucrin P_1) the absolute configuration was determined by the Bijvoet method.

The determination of CD curves also brought substantial improvement to the elucidation of absolute stereochemistry. Positive Cotton effect, associated with the α,β-unsaturated γ-lactone ring [40], occurred in teucvin. Negative Cotton effect was observed for teucvidin and teuflidin, due to the enantiomeric chromophore [41]. Again negative Cotton effect, but of greater intensity, was given by the same chromophore [41] for teuflin and teucrin H_4: the greater values are ascribed to the increased distortion of the γ-lactone ring, due to the 6α-H/10β-H trans relationship.

In the case of gnaphalin, 19-acetyl-gnaphalin, gnaphalidin and fruticolone, the negative CD curve is associated with a C-6 ketone of a normal steroid A/B trans junction, provided that ring B is in a chair conformation; negative CD curves occurred also for suitable C-6 keto derivatives of teucrin A and teucrin E. By contrast, eriocephalin having ring B in a boat conformation showed a positive CD curve. Isofruticolone gave a negative CD curve, due to the C-1 ketone of a normal steroid A/B trans junction.



[40]



[41]

CONCLUSIONS.

At the present point of research, a preliminary statement can be made. About fifteen species of Teucrium have been investigated out of the 300 claimed[39] to exist (but probably many of them are synonimous). Thirty-two new diterpenoids have been isolated and their structures elucidated, whereas for three or four substances structure has not been given or is not sure. All possess the clerodane or 19-norclerodane skeleton, and all are likely to have the ent-clerodane absolute configuration.

With new species being collected in sufficient amount, the chemotaxonomic investigation will be expanded to provide a larger knowledge of the whole genus. Further studies will be concerned with correlation and elucidation of the absolute stereochemistry for all the Teucrium diterpenoids. Finally, the total synthesis of some of these clerodanes will offer a stimulating challenge.

Occurrence of diterpenoids in Teucrium species

T.viscidum subsp.miquelianum	teucvin, teucvidin, teuflin
T.chamaedrys	teucrin A, teucrin B, teucrin C, teucrin D, teucrin E, teucrin F, teucrin G
T.cubense	teucvin
T.flavum	teuflidin, teuflin
T.eriocephalum	eriocephalin
T.gnaphalodes	gnaphalin, 19-acetyl-gnaphalin, gnaphalidin, teucrin P_1
T.spinosum	teuspinin, 19-acetyl-teuspinin, 19-acetyl-gnaphalin
T.fruticans	fruticolone, isofruticolone, 8β-hydroxy-fruticolone
T.homotrichum	eriocephalin, 19-acetyl-gnaphalin
T.intricatum	teucvin
T.scorodonia subsp.euganeum	teuflin
T.montanum	*montanin-A*, *montanin-B*, *montanin-C*, *montanin-D*
T.hyrcanicum	teuflidin, teucrin H_2, 19-acetyl-gnaphalin, teucrin H_4
T.polium subsp. ?	picropolin, 6-acetyl-picropolin, isopicropolin
T.polium subsp. ?	teucrin P_1, teucrin P_2
T.polium subsp. ?	teucrin P_1, montanin-B, 19-acetyl-gnaphalin, teupolin-I, teupolin-II
T.polium subsp.capitatum	picropolin, 19-acetyl-gnaphalin, diosphenol
T.polium subsp.aureum Sicily	teucrin P_1, gnaphalidin
T.polium subsp.aureum Spain	19-acetyl-gnaphalin, auropolin
T.fragile	teugin

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