CONFIGURATION OF NATURAL 9-HYDROXYFUROEREMOPHILANE, ITS 9-HYDROXY EPIMER AND FURANOPETASIN: NMR AND CD STUDIES*, **

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The conformation and configuration analysis of *cis*- and *trans*-furoeremophilanes with hydroxy group in position 9, using ^{1}H NMR and CD spectra, is discussed. Some steroid derivatives were used as models for CD study. A combination of both spectral methods gives complementary results. For natural 9-hydroxyfuroeremophilane the configuration 9β-OH was unequivocally proved and the originally proposed structure of furanopetasin corrected to *VII*.

Since our first communications[2-6] describing the existence of furoeremophilanes in the plants of the *Senecioneae* tribe from the *Asteraceae* family, this group of secondary metabolites has much increased and at present about 200 naturally occurring furoeremophilanes are known in addition to a number of compounds formed by subsequent transformations[7-9]. Along with our own contribution, Japanese teams have the merit extending the knowledge of these substances[10,11]. However, the prolific contribution of Bohlmann should be stressed, who investigated hundreds of plant species, primarily a large number of the species of *Senecio*, *Euryops* and other genera (*e.g.* refs[12-14]).

For the structure determination predominantly spectral methods were employed, mainly ^{1}H and ^{13}C NMR spectroscopy. A large number of substances were correlated by total syntheses[8,9]. In the majority of cases the use of NMR afforded sufficient data and evidence even for the determination of the configurations of the substituents present. Considerable difficulties arose in the determination of the configuration of natural 9-hydroxy derivatives. The problem is inherently connected

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with the flexibility of the *cis*-decalin system of furoeremophilanes, which may assume various conformations in dependence on the position and the stereochemistry of the substituents.

^{1}H NMR *Spectra Discussion*

For the determination of the configuration of the 9-OH group by means of ^{1}H NMR spectroscopy the measurement of the chemical shifts and the coupling constants is available, in principle. While in furoeremophilanes with *trans*-annellated rings A and B (*e.g. I–III*) a rather rigid system with a single well defined conformation is present, in the case of *cis*-derivatives (*e.g. IV–VI*) a flexible system must be taken

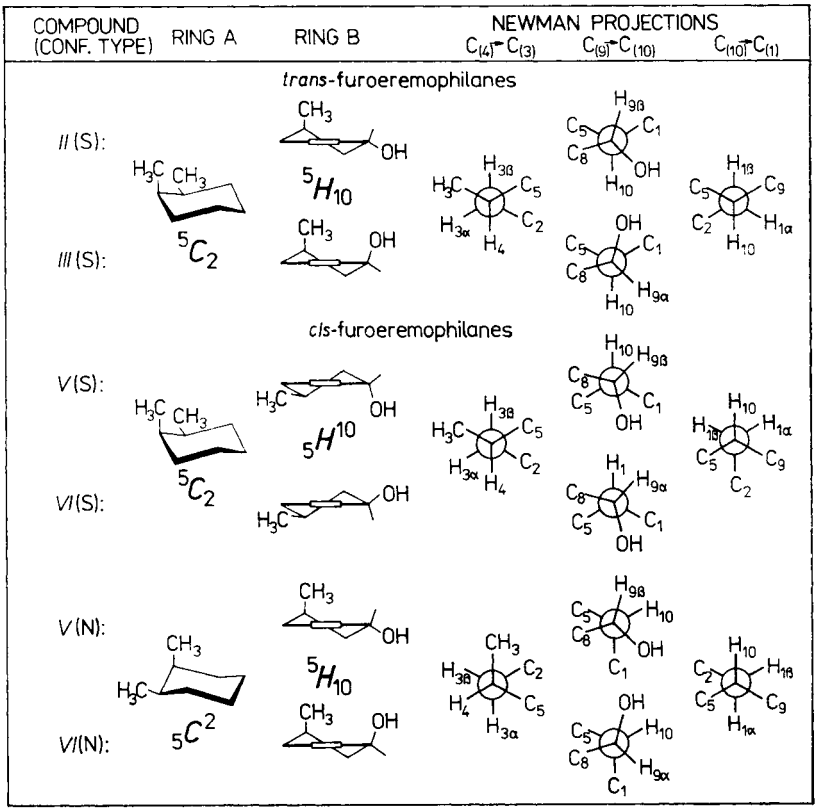
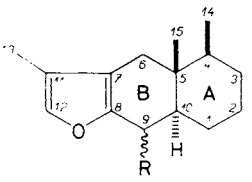


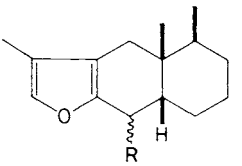
FIG. 1

Possible conformations of *trans*- and *cis*-furoeremophilanes with α or β configuration of the 9-OH group

into consideration, which may assume at least two different conformations. The problem of the configuration of 9-OH thus becomes conformationally dependent, and in order to solve it the conformation of the molecule must be determined first. This situation is illustrated in Fig. 1, showing the possible conformations of the molecules of *trans*- and *cis*-furoeremophilanes with α- or β-configuration of the OH group, the conformations of the rings A and B, and the Newmann projections around the $C_{(4)}$—$C_{(3)}$, $C_{(9)}$—$C_{(10)}$, and $C_{(10)}$—$C_{(1)}$ bonds. The conformations with the chair form of the cyclohexane ring A, the equatorial $C_{(4)}$—CH_3 and the axial $C_{(5)}$—CH_3 groups, *i.e.* of the ${}^5C_2$ type, are indicated as steroidal (S), while the conformations with the chair form of the ring A, the axial $C_{(4)}$—CH_3 and the equatorial $C_{(5)}$—CH_3, *i.e.* of the ${}_5C^2$ type, are indicated as non-steroidal (N). The cyclohexene ring B may adopt the half-chair conformations ${}^5H_{10}$ and ${}_5H^{10}$.



I, R = H
II, R = α-OH
III, R = β-OH



IV, R = H
V, R = α-OH
VI, R = β-OH

The ^{1}H NMR parameters of *trans*-furoeremophilanes *I*—*III* and *cis*-furoeremophilanes *IV*—*VI* are presented in Table I. It is evident, that the 9-OH group causes changes in the majority of assignable signals, with the exception of hydrogens H-13 of furan methyl. The signal of the furan hydrogen H-12 is shifted downfield by 0·1 ppm on introduction of the hydroxy group, which may be explained by charge-transfer effect.

trans-Furoeremophilanes: Stereochemical implications are relatively simple in the *trans*-series (Fig. 1), where compounds *I*—*III* have the same steroidal conformation (S) with the rings A and B in ${}^5C_2$ and ${}^5H_{10}$ forms. The *trans*-annellation of the rings A and B is indicated by the upfield shifts of the angular methyl $C_{(5)}$—CH_3 with respect to *cis*-derivatives (by 0·16 to 0·19 ppm). This effect is known from the steroid series[16,17], where, *e.g.*, the difference of the $C_{(10)}$—CH_3 shifts between 5α- and 5β-androstanes is 0·13 ppm. A similar effect was also observed in the furoeremophilane series[18,19] and in eremophilanolide[20]. In the 9β-OH derivatives the hydroxyl is pseudoaxial and it is in quasi-1,3-diaxial arrangement with the angular $C_{(5)}$—CH_3. Hence, the van der Waals deshielding effect may be expected and thus a downfield shift of $C_{(5)}$—CH_3. The observed downfield shift, 0·2 ppm in *III*, in

contrast to *II*, is thus in agreement with the assigned 9β-OH confiugration in compound *III*. This assignment is further corroborated by the observed coupling constants $J(9, 10) = 8$ Hz in *II* and 3·5 Hz in *III*, which are in a good agreement with the torsion angles 165° in *II* and 45° in *III*, determined from Dreiding models. The chemical shifts of hydrogens H-9 are in accordance with the expected effect of the anisotropy of the shielding field of the unsaturated system – the pseudoequatorial hydrogen H-9α of the 9β-OH derivative *III* should be located at a lower field than the pseudoaxial hydrogen H-9β of the 9α-OH derivative *II* (compare δ 4·52 as against δ 4·17 in *III* or *II*, respectively). Similarly the signals may be assigned to the hydrogens on $C_{(6)}$ – *i.e.* the upfield signal to the pseudoaxial hydrogen H-6α

TABLE I

^{1}H NMR parameters of stereoisomeric furoeremophilanes and their 9-hydroxy derivatives

Protons	*trans*			*cis*		
	I[a]	*II*	*III*	*IV*	*V*	*VI*
			Chemical shifts			
H-6α	*b*	2·05	1·96	*b*	1·72	2·63
H-6β	*b*	2·36	2·46	*b*	2·80	1·96
H-9α	*b*	—	4·52	*b*	—	4·56
H-9β	*b*	4·17	—	*b*	4·79	—
H-12	7·00	7·10	7·12	7·02	7·11	7·12
H-13	1·89	1·88	1·90	1·88	1·89	1·91
H-14	0·94	0·86[c]	0·88[d]	0·94	1·03	0·89
H-15	0·70	0·68	0·88	0·88	0·87	1·04
			Coupling constants[e]			
J(6α,6β)	*b*	15·5	15·8	*b*	16·0	16·5
J(6α, 9α)	*b*	—	<0·5	*b*	—	0
J(6α, 9β)	*b*	≈0	—	*b*	≈0	—
J(6α, 15)	*b*	0·7	0·7	*b*	0·7	0
J(6β, 9α)	*b*	—	≈0	*b*	—	1·2
J(6β,9β)	*b*	≈1	—	*b*	2·0	—
J(9, 10)	*b*	8·0	3·5	*b*	5·0	4·5
J(12, 13)	1·0	1·2	1·2	1·3	1·2	1·2
J(4, 14)	7·0	*b*	≈6·5	7·0	7·0	6·5

[a] Data taken from ref.[15]; [b] the values were not determined; [c] second order multiplet with splitting 5·5 Hz; [d] partially overlapped with H-15; [e] the absolute values of coupling constants are given.

and the low-field signal to the pseudoequatorial hydrogen H-6β. This assignment is corroborated by the observed non-zero long-range coupling (W-type)[21] between the upfield signal of H-6α and the angular $C_{(5)}$—CH_3. The methyl signal is split to a doublet with J about 0·7 Hz in *II* and *III*; an analogous long-range coupling is also known from the field of steroids, *i.e.* between the axial H-1α or H-12α and the angular methyls 19 or 18 (refs[22,23]). The assigned configurations of 9-OH also agree with the observed homoallylic couplings between the hydrogens H-9 and H-6. It is known that this interaction has maximum for C—H bonds of coupled hydrogens if they make an angle of 90° with the plane of the double bond, and gives zero-value for angles close to 0°. The interaction between H-9 and H-6, observed only in 9α-OH derivative *II*, where H-9 is pseudoaxial, is in agreement with this fact.

cis-Furoeremophilanes: Stereochemical implications in the *cis*-series (compounds *IV*–*VI*) are more complex (see Fig. 1), because the compounds can assume both steroidal (S) and non-steroidal (N) conformation with the rings A and B in $^5C_2$,

TABLE II

Characteristic stereochemical features and the expected interproton coupling constants in 9-hydroxyfuroeremophilanes

Parameter	Annellation A/B					
	trans		*cis*		*cis*	
Conformation	steroidal		steroidal		non-steroidal	
Ring A	$^5C_2$		$^5C_2$		$_5C^2$	
Ring B	$^5H_{10}$		$_5H^{10}$		$^5H_{10}$	
Substituent	9α-OH	9β-OH	9α-OH	9β-OH	9α-OH	9β-OH
H-9[a]	ax′	eq′	eq′	ax′	ax′	eq′
Φ(9, 10)	165°	45°	45°	165°	45°	75°
J(9, 10)	~10	~5	~5	~10	~5	~1
H-4[a]	ax		ax		ax	
J(4, 3α)	~3		~3		~3	
J(4, 3β)	~12		~12		~3	
H-10[a]	ax		eq[b]		ax[b]	
J(10, 1α)	~3		~3		~12	
J(10, 1β)	~12		~3		~3	
H-14 (C_4)—CH_3)[a]	eq		eq		ax	
H-15 ($C_{(5)}$—CH_3)[a]	ax		ax[b]		eq[b]	
J(15, 6α)	1		0		1	

[a] ax axial, eq equatorial, ax′ pseudoaxial, eq′ pseudoequatorial; [b] the orientation of the angular H-10 and $C_{(5)}$—CH_3 in *cis*-derivatives is reversed if we use the cyclohexene ring B as a reference.

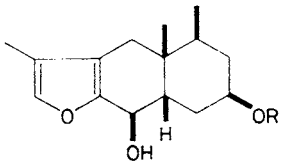
${}_5H^{10}$ or ${}_2C^5$, ${}^5H_{10}$ forms, respectively, or they can also exist as equilibrium mixtures of both forms. The discrimination of both forms can be carried out theoretically on the basis of vicinal coupling constants of hydrogens in positions $C_{(4)}$ and $C_{(3)}$ or $C_{(10)}$ and $C_{(1)}$ – see Table II. However, these data are difficult to obtain for compounds *IV*–*VI* and a number of further furoeremophilanes, since the hydrogens H-4 and H-10 form with other hydrogens poorly resolved multiplets in the upfield part of the spectra (at least on frequencies lower than 200 MHz). In compound *IV* the low-field shift of the angular methyl $C_{(5)}$—CH_3 in contrast to *I* indicates *cis*-annellation of the rings (see above). The position of the secondary methyl $C_{(4)}$—CH_3 remains the same as in *I*, which can be explained by the fact that in both substances it assumes the same equatorial position in the same conformation ${}^5C_2$. Since $C_{(4)}$—CH_3 is a peripheral but not an angular substituent, it may be expected that it will be affected by the anisotropy of the ring A. Thus, the conformation change ${}^5C_2 \rightarrow {}_2C^5$ during the transition from (S) to (N) conformation will cause a change in the chemical shift (*e.g.* in methylcyclohexanes the equatorial methyl appears at a higher field than the axial methyl[24,25]). An application of these considerations to 9-OH derivatives *V* and *VI*, and a comparison of their shifts $C_{(4)}$—CH_3 (δ 1·03 or 0·89) show that they should have different conformations. While δ 0·89 for *VI* is in good accord with the values δ 0·90 for equatorial $C_{(4)}$—CH_3 in ${}^5C_2$ form of ring A, found for compounds *I*–*IV*, the value δ 1·03 indicates the presence of an axial $C_{(4)}$—CH_3 group (see methylcyclohexanes above) and hence a ${}_5C^2$ conformation of the ring A. This means that the 9α-OH derivative *V* should assume the non-steroidal conformation (N) with the rings A and B in ${}_5C^2$ and ${}^5H_{10}$ forms, while the 9β-OH derivative *VI* should be, similarly as in *IV*, in steroidal conformation (S) with rings A and B in ${}^5C_2$ and ${}_5H^{10}$ forms.

The position of the angular methyl $C_{(5)}$—CH_3 in *V* and *VI* can be affected again by the orientation of the ring A and the anisotropy of the shielding field of the C=C bond. The higher value of δ 1·04 in *VI* is in agreement with the axial position with respect to ring A in ${}^5C_2$ conformation, and the lower value δ 0·87 in *V* with the equatorial position in ${}_5C^2$ form, and the difference of the anisotropic shielding in the ${}_5H^{10}$ or ${}^5H_{10}$ form should have the same trend. The observed characteristic long-range coupling between $C_{(5)}$—CH_3 and the pseudoaxial H-6 in derivative *V* (J = 0·7 Hz), for which suitable conditions exist only in non-steroidal conformation (N), confirms the correctness of the conformational assignment. The reason for the destabilization of the steroidal conformation in 9α-OH derivative may consist in steric interactions of the pseudoaxial 9α-OH with the axial hydrogens H-4 and H-2 which disappear on transition to the non-steroidal conformation with the pseudoequatorial 9α-OH. In contrast to this, in the 9β-OH derivative the steric interaction of the pseudoaxial 9β-OH with the angular $C_{(5)}$—CH_3, leading to the preference of the steroidal conformation, may represent the destabilizing factor in the non-steroidal conformation.

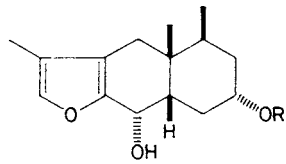
In view of the differing conformations of *V* and *VI*, the determination of the configuration of 9-OH is much more complex than in the case of *trans*-derivatives. The very similar values of the coupling constants found, *i.e.* $J(9, 10) = 5{\cdot}0$ or 4·4 Hz, do not permit an unambiguous configurational assignment of the hydroxyl group. Another possibility consists in the homoallylic coupling between the hydrogens on $C_{(6)}$ and $C_{(9)}$. Here the situation is similar to that in *trans*-derivatives *II* and *III*.

From Table II it follows that the value $J(9, 10) = 5$ Hz for 9α-OH derivative agrees with both conformational types (S) and (N), while for 9β-OH derivative very different values $J(9, 10) = 10$ or 1 Hz for (S) or (N) conformation, respectively, have been derived. This means that in the case of 9β-OH derivative either a distinct distortion of the fragment $C_{(9)}$—$C_{(10)}$ is involved, or — which seems more probable — the observed value $J(9, 10) = 4{\cdot}5$ Hz is caused by the presence of both conformational types which exist in a rapid equilibrium from the point of view of the ^{1}H NMR time scale.

Furanopetasin (VII) *and furanopetasol* (VIII): For furanopetasin and furanopetasol the structures *IX* and *X* were formerly proposed[5,6] with α-configurations of both oxygen-containing substituents in positions 2 and 9. A detailed NMR analysis of the two compounds showed, however, that the correct structures are *VII* and *VIII*, respectively, with the β-configurations of both substituents. The ^{1}H and ^{13}C NMR data are presented in Table III. From the values of the vicinal coupling constants of hydrogens H-4 and H-10 in *VIII* ($J(4, 3) = 3{\cdot}6$ and 11·2 Hz; $J(10, 1) =$ $= 3{\cdot}7$ and 4·2 Hz) and the very similar values found in *VII*, the preferred steroidal conformation for both compounds *VII* and *VIII* can be derived (according to the



VII, R = Ang
VIII, R = H



IX, R = Ang
X, R = H

criteria in Table II). The configuration of the substituent at $C_{(2)}$ can be derived from the vicinal couplings of the H-2. The observed values $J(2, 1) \approx 5$ and 10 Hz; $J(2, 3) \approx$ ≈ 5 and 10 Hz indicate an axial position of H-2, with an equatorial $C_{(2)}$—OR substituent, which in the steroidal conformation of the ring A means β-configuration for $C_{(2)}$—OR. The information concerning the configuration of the hydroxyl at $C_{(9)}$ is included in the $J(9, 10)$. Its value (6·6 Hz in *VII* and 7·6 Hz in *VIII*) is higher than the value expected for 9α-OH derivative in the steroidal and non-steroidal conformation (≈ 5 Hz, see Table II). The actual configuration at $C_{(9)}$ must thus be

9β-OH, for which, however, the value $J(9, 10)$ in steroidal conformation (determined above) should be slightly higher ($\approx$10 Hz). The decrease of the observed value is caused evidently by the partial population of the non-steroidal conformation (with

TABLE III
^{1}H and ^{13}C NMR parameters of furanopetasin (*VII*) and furanopetasol (*VIII*)

Proton	*VII*[a]	*VIII*[a]	*J*(H, H)	*VII*	*VIII*
H-1α	2·10[b]	2·18 bdt	*J*(1α, 1β)	13·0	13·2
H-1β	1·81 ddd	1·69 ddd	*J*(1α, 2)	4·8	5·1
H-2	5·16 m	4·01 m	*J*(1α, 3)	*c*	1·6
H-3α	*d*	1·81 m	*J*(1α, 10)	*c*	3·7
H-3β	1·54 m	1·41 m	*J*(1β, 2)	9·5	10·3
H-4	1·65 m	1·57 m	*J*(1β, 10)	3·8	4·2
H-6α	2·58 dd	2·57 dd	*J*(2, 3α)	4·8	5·4
H-6β	2·12 dd	2·13 dd	*J*(2, 3β)	9·5	9·8
H-9	4·71 bd	4·66 bd	*J*(3α, 3β)	12·5	12·4
H-10	*d*	1·88 dt	*J*(3α, 4)	3·6	3·6
H-12	7·12 dq	7·11 dq	*J*(3β, 4)	10·2	11·2
H-13	1·91 d	1·91 d	*J*(4, 14)	6·6	6·4
H-14	0·88 d	0·84 d	*J*(6α, 6β)	16·4	16·4
H-15	1·10 s	1·07 s	*J*(6α, 9)	1·0	0·9
Angelate			*J*(6β, 9)	1·8	2·2
α-CH_3	1·89 p	—	*J*(9, 10)	6·6	7·6
β-CH_3	1·97 dq	—	*J*(9, 12)	0·7	1·0
CH—	6·01 qq	—	*J*(12, 13)	1·3	1·2

Carbon	*VII*	*VIII*[e]	Carbon	*VII*	*VIII*[e]
C-1	34·71 t	38·47 t	C-11	119·05 s	118·95 s
C-2	69·61 d	65·95 d	C-12	137·20 d	138·48 d
C-3	38·11 t	38·47 t	C-13	7·84 q	7·52 q
C-4	48·30 d	49·88 d	C-14	22·27 q	21·35
C-5	28·29 s	29·93 s	C-15	16·24 q	15·82 q
C-6	29·92 t	29·93 t	Ang: C-16	167·58 s	—
C-7	118·03 s	118·01 s	C-17	128·06 s	—
C-8	148·84 s	148·72 s	C-18	138·85 d	—
C-9	65·06 d	64·31 d	C-19	15·67 q	—
C-10	31·23 d	30·76 d	C-20	20·46 q	—

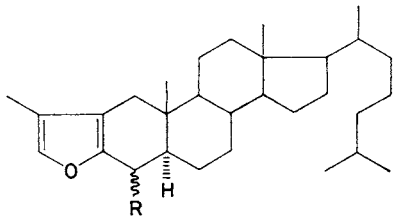
[a] Data taken from the spectrum at temperature 55°C; [b] overlapped by H-6; [c] the value could not be determined; [d] overlapped by angelate methyls; [e] the spectrum was measured in a mixture of C^2HCl_3 and $C^2H_3O^2H$ (2 : 1).

$J(9, 10) \approx 1$ Hz). The calculation based on the values mentioned shows an approximate population of 70% or 80% (in *VII* or *VIII*) of the preferred steroidal conformation in equilibrium. The existence of the indicated conformational equilibrium is also supported by the ^{13}C NMR spectra in which a broadening of the signals of carbons $C_{(1)}$, $C_{(3)}$, $C_{(9)}$, $C_{(14)}$, and especially $C_{(4)}$ and $C_{(10)}$ was observed, with half-widths higher than 20 Hz. In the steroidal conformation of the ring A the substituents in positions 2 and 4 are equatorial, which evidently leads to stabilization of the steroidal form.

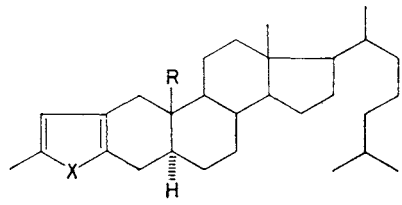
CD *Spectra Discussion*

In order to determine the configuration of natural 9-hydroxyfuroeremophilane (*VI*) and its epimer *V* from their chiroptical data (Fig. 2), we made use of the CD-curves of synthetical model compounds (furano- and thiopheno-steroids *XI*–*XIX*) with known conformation[26,27]. To this end we have to prove: (i) that such model compounds give Cotton effects comparable to those of furoeremophilanes and (ii) that axial C—C bonds on the cyclohexene ring do not drastically change the CD spectra.

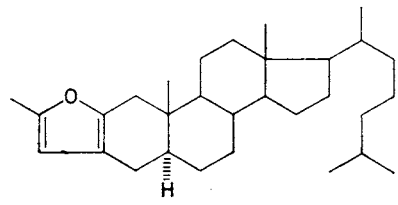
Fig. 3 presents the CD spectra of the two synthetic rigid 9-hydroxy substituted *trans*-furoeremophilanes *II* and *III* together with those of the corresponding model steroids *XI* and *XII*. In all curves two major bands can be seen, but from the



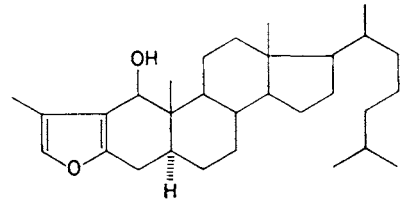
XI, R = α-OH
XII, R = β-OH



XIII, R = CH_3; X = O
XIV, R = H; X = O
XV, R = CH_3; X = S
XVI, R = H; X = S



XVII



XVIII

many model compounds which we had at hand we must conclude, that there are actually up to five bands present between 260 and 180 nm. Although the Δε-va-

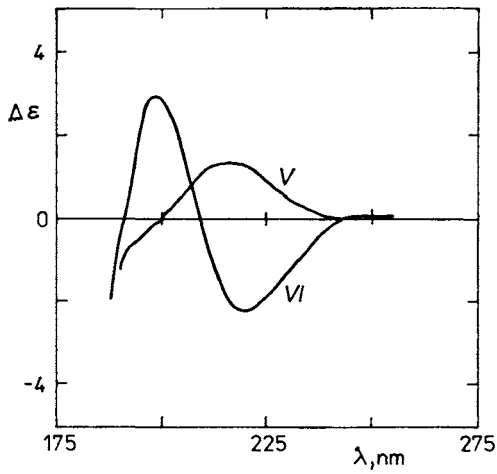


FIG. 2
CD spectra of 9-hydroxy-*cis*-furoeremophilanes *V* and *VI*

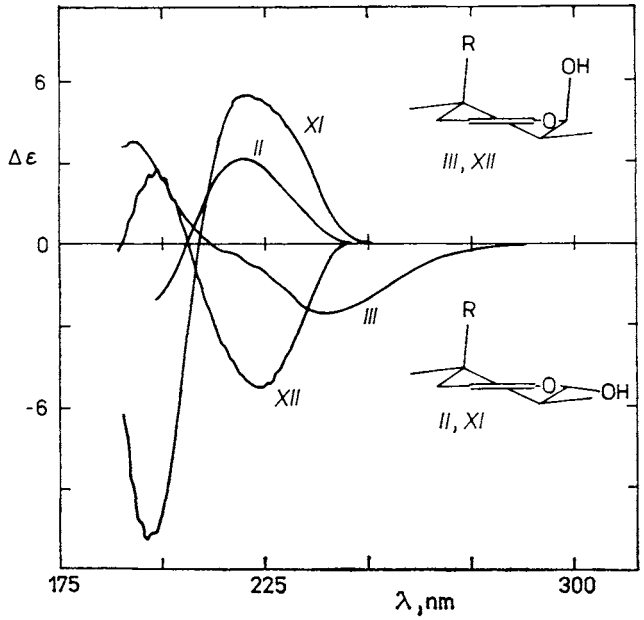
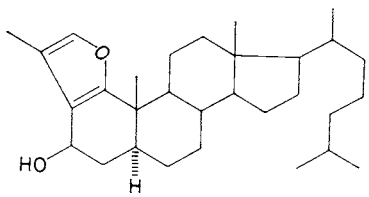
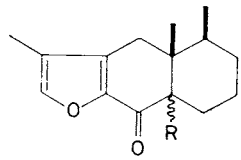


FIG. 3
CD spectra of 9-hydroxy-*trans*-furoeremophilanes *II* and *III* and corresponding furano-steroids *XI* and *XII*

lues differ between the individual compounds of each corresponding pair (in part this difference is due to the different solvents which had to be used) the signs of the respective CD bands are the same for each pair. Furano-steroids can, therefore, be used as model compounds for chiroptical studies, provided they have the same substitution pattern of the furan chromophore.



XIX



XX, R = β-H
XXI, R = α-H

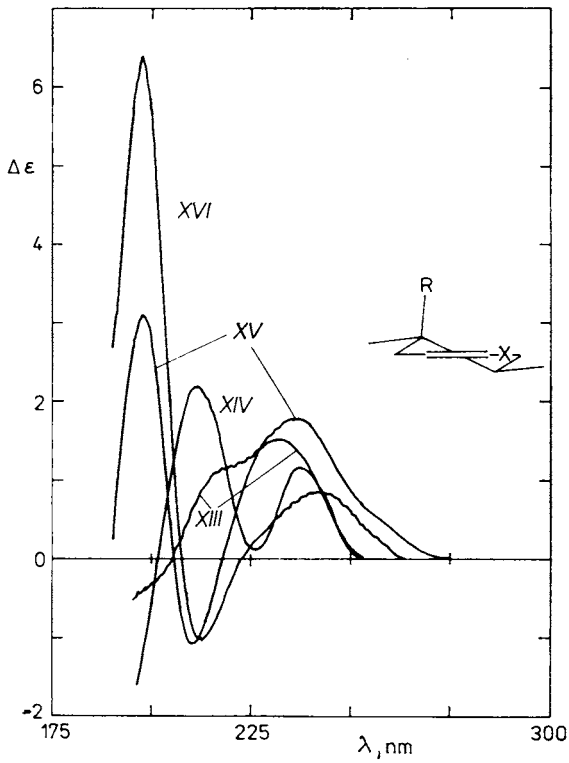


FIG. 4

CD spectra of furano- and thiopheno-steroids *XIII*, *XV* and of their 19-nor derivatives *XIV*, *XVI*

In order to study the influence of axial C—C bonds on the cyclohexene ring, we have compared the CD spectra of different model compounds. The three main Cotton effects of furano-steroid *XIII* have the same signs as those of the 19-nor derivative *XIV* and the same is observed for the corresponding thiophenosteroids *XV* and *XVI* (Fig. 4). The presence or absence of an axial C—C bond* at position 5 of a furoeremophilane influences thus only the magnitudes but not the signs of the Cotton effects.

In order to get informations about the influence of an axial C—C bond at $C_{(10)}$ of a furoeremophilane we compared first the CD spectra of *XIV* and *XVII*. These (together with our "standard projection" along the C_2 axis of the cyclohexene half-chair with the furan oxygen always at the right side) are presented in Fig. 5. Compound *XVII* shows four Cotton effects between 250 and 180 nm, *XIV* has an additional one above 250 nm. Obviously the negative minimum of *XIV* around 230 nm actually corresponds to a small negative Cotton effect which is embedded between two stronger positive ones. If we take this into account then again the three Cotton effects between 250 and 200 nm have the same signs for these two analogues.

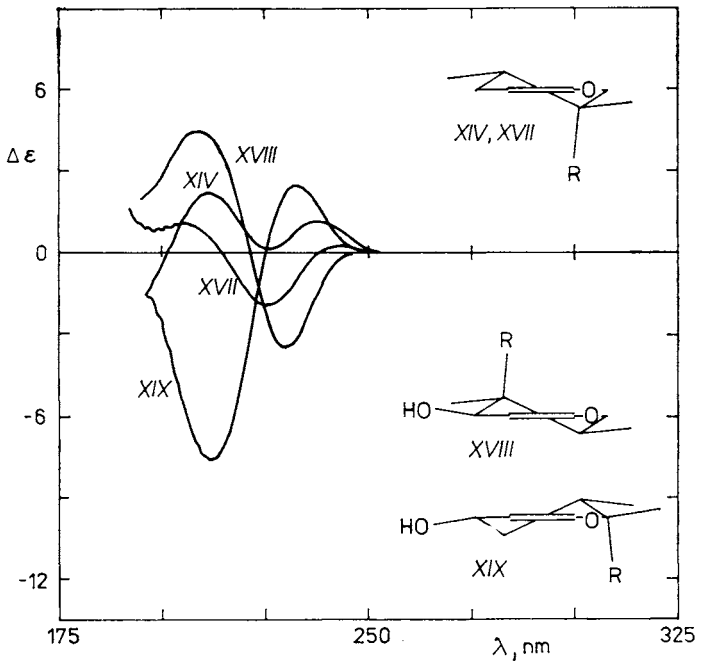


FIG. 5
CD spectra of furano-steroid derivatives *XIV* and *XVII*—*XIX*

* Here and in the following text "axial" always refers to the cyclohexene half-chair ring.

It is thus also proved that an axial C—C bond at $C_{(10)}$ of the furoeremophilane skeleton does not change the signs of the Cotton effects either. This is even better seen by a comparison of the CD spectra of *XVIII* and *XIX*, whose (furan + cyclohexene)-moieties are enantiomeric to each other as is the arrangement of the nearby hydroxy groups. These two curves are indeed enantiomorphic to each other (Fig. 5) irrespective of the completely different substitution pattern of the cyclohexene ring by C—C bonds. This shows again the well documented fact that a perturber next to a chromophore together with the helicity of the attached ring ("second-sphere") determine mainly the Cotton effects.

In discussing now the CD spectra of the *cis*-furoeremophilanes *V* and *VI* we have to take into account the possible flexibility of the ring system. Whereas the energy

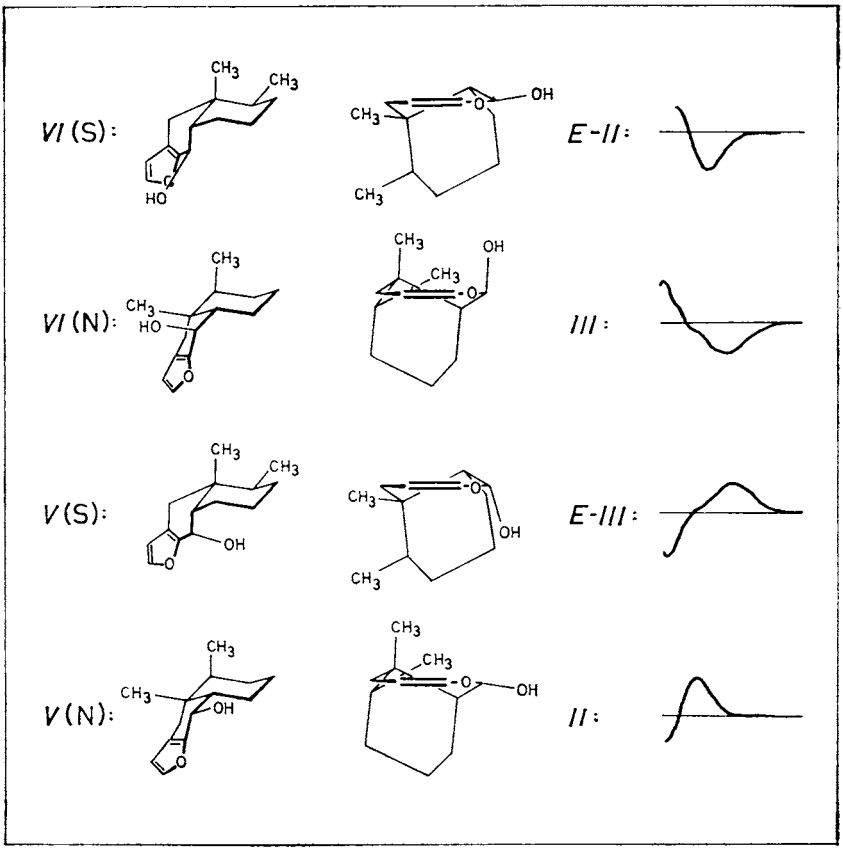


FIG. 6

The possible conformations in 9-hydroxy-*cis*-furoeremophilanes and the corresponding CD curves

difference between a boat-like and half-chair conformation of the cyclohexene is by no means as large as between a boat and chair form of a cyclohexane, nevertheless the annellation with the second cyclohexane ring in a furoeremophilane renders the half-chair in such a molecule much more favourable than the boat-like conformation. Two conformations have thus to be discussed for both *V* and *VI*, although deviations from the "classical" half-chair form might be possible. In Fig. 6 two different stereoprojections are shown for each of the molecules in question. From these it is obvious that *VI* should mainly be present in the steroidal conformation and *V* in the non-steroidal one. If we now take into account that axial C—C bonds do not change the signs of the individual Cotton effects, then the steroidal conformation *VI*(S) of *VI* should give a CD comparable to that of the enantiomer *E-II* of *II*, its non-steroidal conformation *VI*(N) is comparable to that of *III*. Analogously the CD of *V*(S) should resemble that of *E-III*, and that of *V*(N) the CD of *II*. From Fig. 6 it can thus be seen that only the shapes, but not the signs of the Cotton effects are affected by the conformation, as long as we have the same absolute configurations at $C_{(5)}$ and $C_{(10)}$. As these are, however, known to be both β, a CD curve with negative Cotton effect above 200 nm and positive one below this wavelength is consistent only with the 9β-hydroxy configuration of *VI*, whereas the CD curve with the opposite signs must belong to the 9α-hydroxy configuration of *V*. CD Spectra prove, therefore, unequivocally that natural 9-hydroxy-furoeremophilane must have structure *VI*. However, at the moment no firm conclusion can be drawn about the proportion of the (S) to (N) form of *VI* or *V* from their chiroptical data.

Furanopetasin (*VII*) is a sesquiterpene ester, whose structure has been determined as 2β-angeloyloxy-9β-hydroxy-*cis*-furoeremophilane mainly from ^{1}H NMR studies. Its CD should, therefore, resemble that of *VI*, and this is indeed the case (Fig. 7).

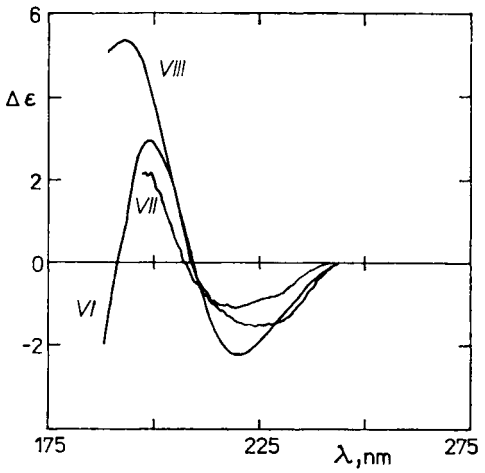


FIG. 7

CD spectra of furanopetasin (*VII*), furanopetasol (*VIII*), and natural 9-hydroxyfuroeremophilane (*VI*)

Also furanopetasol (*VIII*), the corresponding sesquiterpene diol, shows a similar CD curve. Any chiral interaction between the strong $\pi \rightarrow \pi^*$-moment of the angeloyl moiety and the transition moments of the furan ring is thus negligible.

EXPERIMENTAL

The melting points were determined on a Kofler block and are not corrected. The molecular masses were determined by mass spectroscopy on an AEI MS 902 instrument. The ^{1}H NMR and ^{13}C NMR spectra were recorded with a Varian XL-200 spectrometer in deuteriochloroform with tetramethylsilane as internal standard. CD spectra were recorded by Dichrograph Mark III from Jouan–Jobin–Yvon with a joint PDP-8 computer. The sample concentration was c. 1 mg. . ml^{-1} and the cell layer from 0·02—2·00 cm. For thin-layer chromatography Kieselgel GF_{254} or DSC-alumina sheets from Merck were used, layered with Kieselgel 60 F_{254}. For detection cerium sulphate–molybdatophosphoric acid, chromosulphuric acid or sulphuric acid with heating by flame were used, respectively. The preparative column chromatography was carried out on Kieselgel (Hermann, Köln), desactivated with 13% of water. For the synthesis of model compounds *XI*—*XIX* cholesterol was used as starting material. All compounds and their intermediates were fully characterized spectroscopically or by direct comparison with authentic samples[26,27]. Their synthesis was fully described[26,27].

9β-Hydroxy-10β*H*-furoeremophilane (*VI*)

The 9-Hydroxyfuroeremophilane containing a fraction (24·5 g) obtained from the light petroleum extract of dry ***Petasites*** hybridus rhizomes[6], monitored by thin layer chromatography with an authentic sample, was further fractionated on a column of alumina (750 g, activity grade III, Reanal, Hungary) using a solvent mixture of light petroleum and benzene with a concentration gradient 10 : 0 (3 l), 4 : 1 (3 l), 1 : 1 (2 l), 0 : 10 (1 l). From the fractions, monitored by thin-layer chromatography, crude 9-hydroxyeremophilane (7 g) was collected. The crude product was distilled in a vacuum (7 Pa) at 145°C (bath temperature). The first fraction (2·1 g) crystallized after 24 h standing; m.p. 58—61°C. According to TLC, IR, and NMR the compound was identical with the authentic sample[4]. For ^{1}H NMR see Table I.

9-Oxo-10β*H*-furoeremophilane (*XX*)

Crude 9β-hydroxy-10β*H*-furoeremophilane (*VI*; 500 mg) was dissolved in pyridine (5 ml) and a solution of chromium trioxide (500 mg) in pyridine (5 ml) and water (0·5 ml) was added to it. After 4 h standing at room temperature, the mixture was poured into water and extracted with diethyl ether. The ethereal phase was washed with tartaric acid solution, dried over magnesium sulphate and evaporated. The product was chromatographed on a column of silicagel (100 g) with benzene. A chromatographically pure fraction was recrystallized from pentane yielding 200 mg of *XX* with m.p. 114—115°C identical according to TLC, IR, and NMR with the authentic sample[6].

Compound *XX* was also obtained by the same procedure as in ref.[6] using pure *VI* as starting material.

9α-Hydroxy-10β*H*-furoeremophilane (*V*)

A solution of lithium aluminium hydride (200 mg) in diethyl ether (20 ml) was added dropwise to a solution of 9-oxo-10β*H*-furoeremophilane (*XX*; 100 mg) in diethyl ether (5 ml) and the

mixture was stirred at room temperature for 1 h. After decomposition of the excess of hydride with ethyl acetate (5 ml) and water (5 ml) the mixture was acidified with 1M-H_2SO_4 and extracted with ether. The ethereal phase was dried over magnesium sulphate and evaporated. After purification on a short column of silicagel with benzene–methanol–ethyl acetate (100 : 2 : 1) the noncrystalline compound was characterized by ^{1}H NMR (Table I) and by CD (Fig. 2). For $C_{15}H_{22}O_2$ (234·3) calculated: 76·88% C, 9·46% H; found: 76·78% C, 9·55% H.

9-Oxo-10α*H*-furoeremophilane (*XXI*)

9-Oxo-10β*H*-furoeremophilane (*XX*; 250 mg) was dissolved in ethanol (2 ml) and 5% ethanolic solution of potassium hydroxide was added. The mixture was heated at 70°C under nitrogen for 30 min, then acidified with 1M-H_2SO_4. After 10 min standing water was added and the mixture extracted with diethyl ether. The combined ethereal extracts were dried and evaporated. After purification on a short column of silicagel with benzene–methanol–ethyl acetate (100 : 2 : 1) the product crystallized from pentane with m.p. 148—150°C. According to TLC, IR, and NMR the compound was identical with the authetnic sample[28].

9α-Hydroxy-10α*H*-furoeremophilane (*II*) and 9β-hydroxy-10α*H*-furoeremophilane (*III*)

9-Oxo-10α*H*-furoeremophilane (*XX*; 200 mg) was dissolved in diethyl ether (5 ml) and a solution of lithium aluminium hydride (200 mg) in diethyl ether (20 ml) was added dropwise to it. The mixture was refluxed for 30 min and then decomposed with aqueous sodium sulfate solution, acidified with 1M-H_2SO_4 and extracted with diethyl ether. After evaporation of the solvent, the residue was chromatographed on a silica gel column with the solvent system light petroleum–diethyl ether (9 : 1). Two fractions were obtained. The first one crystallized and gave compound *III* with m.p. 84—87°C, characterized by ^{1}H NMR (Table I) and CD (Fig. 3) spectra. For $C_{15}H_{22}O_2$ (234·3) calculated: 76·88% C, 9·46% H; found: 76·69% C, 9·57% H. The second fraction gave noncrystalline compound *II* characterized by ^{1}H NMR (Table II) and CD (Fig. 3) spectra.

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