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# GRIESENIN AND DIHYDROGRIESENIN, TWO NEW SESQUITERPENOID LACTONES FROM *GEIGERIA AFRICANA* GRIES—II

## NUCLEAR MAGNETIC RESONANCE STUDIES AND CONFORMATION

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**Abstract**—The NMR spectra of griesenin (I) and dihydrogriesenin (II), sesquiterpenoid lactones from *Geigeria africana* Gries, and some of their derivatives have been analysed in detail. The conformation of the cycloheptene ring has been determined to be a slightly distorted boat. The NMR parameters are discussed in relation to the stereochemistry.

## INTRODUCTION

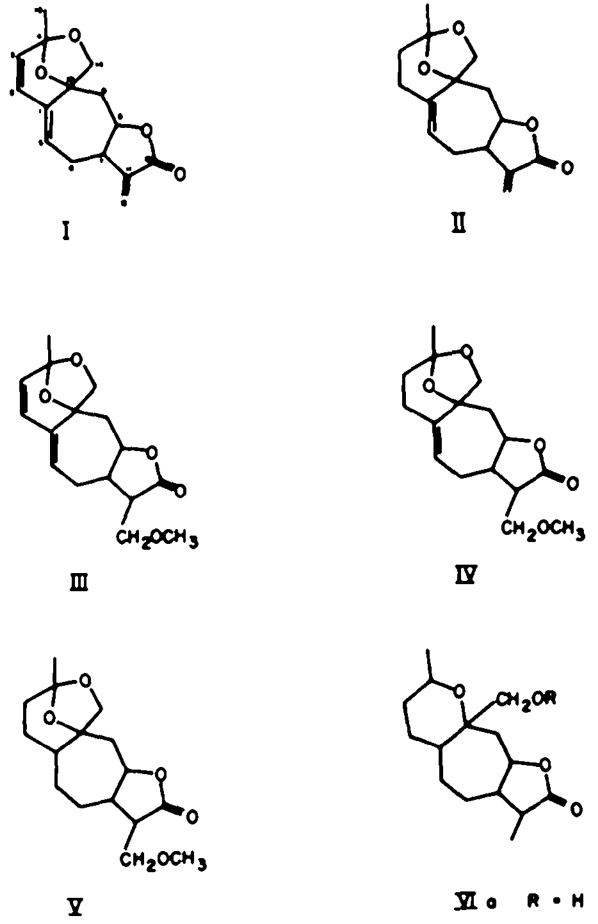
Although NMR spectroscopy is used extensively in most structure investigations, only relatively few spectra of complex compounds have been completely analysed. This, however, is of importance for the correlation of NMR parameters and the stereochemistry of organic compounds. We have therefore performed a detailed analysis of the NMR spectra of the two sesquiterpenoid lactones griesenin (I) and dihydrogriesenin (II), the structures of which have been reported in the preceding paper,[1] and some of their derivatives.

## ASSIGNMENTS AND ANALYSIS

The 100 MHz NMR spectrum of griesenin (I) is reproduced in Fig. 1. The exocyclic methylene protons of the $\gamma$-lactone ring gave rise to the two characteristic doublets[2] at $\tau = 3{\cdot}74$ and $4{\cdot}31$ with splittings of 2·0 and 1·6 Hz, respectively, due to allylic interactions with the proton on C-7.[3–5] The olefinic protons H-2 and H-3 appeared as an AB-pattern with individual resonances at $\tau = 4{\cdot}00$ and $4{\cdot}17$ ($J_{2,3} = 9{\cdot}4$ Hz). The latter was assigned to the proton on C-2 because of observable long-range couplings to the protons H-5 and H-6 ($J = 0{\cdot}7$ and $0{\cdot}8$ Hz). The origin of these couplings has been established by spin decoupling. The remaining olefinic proton in griesenin (H-5) appeared as a 4-line pattern at $\tau = 4{\cdot}35$ with splittings of 9·0 and 3·4 Hz caused by the adjacent methylene group (C-6).

The proton next to the ether oxygen of the $\gamma$-lactone ring usually absorbs between $\tau = 5{\cdot}0$–$6{\cdot}0$ in sesquiterpenoid lactones of similar structure.[6–8] In gafrinin[5] and xanthumin[9] it occurred at $\tau = 5{\cdot}37$ and $5{\cdot}30$, respectively. The 7-line pattern at $\tau = 5{\cdot}37$ was thus assigned to the proton on C-8. The splittings of 5·2, 7·1 and 11·9 Hz arise from interactions with the protons on C-7 and C-9. When the H-7, H-8 coupling (7·1 Hz) is removed, the pattern reduces to the four-line X-part of an ABX-system.[10] The corresponding AB-part is identified with the aid of the other two splittings. An ABX-analysis yielded: $\tau_{9_{eq}} = 7{\cdot}54$, $\tau_{9_{ax}} = 7{\cdot}29$, $\tau_8 = 5{\cdot}37$; $J_{9_{eq},9_{ax}} = 12{\cdot}9$ Hz, $J_{8,9_{eq}} = 4{\cdot}9$ Hz, $J_{8,9_{ax}} = 11{\cdot}8$ Hz.

FORMULA SCHEME



I

II

III

IV

V

VI a R = H
VI b R = Ac

The proton H-7 appeared as a complex pattern at $\tau = 6{\cdot}82$. The multiplicity results from couplings with the protons on C-6 and C-8 and the exocyclic methylene group. The H-6 protons at $\tau = 7{\cdot}34$ (overlapping with the H-9 protons) and at $\tau = 7{\cdot}83$ have been analysed as the AB-part of an ABXY-system[11] with the protons H-5 and H-7 as X- and Y-parts, respectively. This gave: $J_{6eq,6ax} = 16{\cdot}7$ Hz, $J_{5,6ax} = 3{\cdot}3$ Hz, $J_{5,6eq} = 9{\cdot}1$ Hz, $J_{6ax,7} = 12{\cdot}7$ Hz, $J_{6eq,7} = 3{\cdot}6$ Hz and $J_{5,7} = 0{\cdot}0$ Hz.

The AB-pattern with $\tau_A = 6{\cdot}12$, $\tau_B = 6{\cdot}23$, and $J_{AB} = 7{\cdot}2$ Hz was attributed to the methylene protons on C-14. The C-4 Me gave a singlet at $\tau = 8{\cdot}44$.

These assignments have been confirmed by decoupling experiments. Irradiating at $\tau = 6{\cdot}82$ collapsed the exocyclic methylene proton signals to singlets and at the same time changed the patterns at $\tau = 5{\cdot}37$, $7{\cdot}34$, and $7{\cdot}83$. Decoupling H-8 at $\tau = 5{\cdot}37$ simplified the patterns at $\tau = 6{\cdot}82$, $7{\cdot}29$, and $7{\cdot}54$.

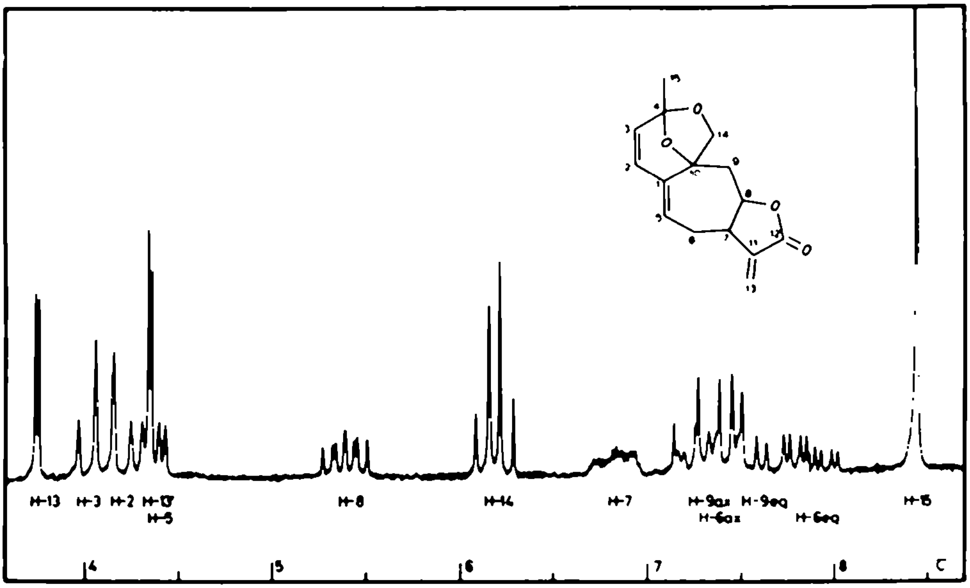


FIG. 1 100 MHz Spectrum of Griesenin

When the proton H-2 at $\tau = 4{\cdot}17$ was irradiated the H-6 proton at $\tau = 7{\cdot}34$ sharpened considerably, but the effect on the quartet at $\tau = 4{\cdot}35$ could not be recorded as the chemical shift difference between H-2 and H-5 is too small. Decoupling the signal at $\tau = 7{\cdot}34$ removed one of the small splittings in the H-2 resonance and collapsed the H-5 quartet to a doublet with a $9{\cdot}0$ Hz spacing. The low-field part of the H-14 pattern appeared slightly broader indicating some unresolved long-range coupling. In the alcohol VIa and its acetate this long-range interaction over four saturated bonds is remarkably stronger and splittings of $1{\cdot}7$ Hz are measured in the low-field H-14 proton and the pseudo-axial H-9 proton of the alcohol.

The NMR parameters obtained for compounds I–VI are summarized in Table 1.

TABLE 1. NMR DATA ON GRIESENIN.

| Protons | Compounds I | | II | | III | |
|---|---|---|---|---|---|---|
| H-2 | 4·17 (B) | | ~7·84 (c) | | 4·20 (A) | |
| | | $J_{2,3}$ = 9·4 | | | | |
| | | $S_{2,5}$, $S_{2,6ax}$ 0·8, 0·7 | | | | $J_{2,3}$ = 9·5 |
| H-3 | 4·00 (A) | | ~8·25 (c) | | 4·02 (B) | |
| H-4 | — | | — | | - | |
| H-5 | 4·35 (X) | $J_{5,6}$ = 3·3 | 4·46 (X) | $S_{5,6ax}$ = 3·2 | 4·38 (c) | $S_{2,5}$ = 2·5 |
| | | $J_{5,6eq}$ = 9·1 | | $S_{5,6eq}$ = 9·1 | | $S_{5,6eq}$ = 8·3 |
| | | $J_{6ax,6eq}$ = 16·7 | | $J_{6ax,6eq}$ = 15·3 | | $S_{5,6ax}$ = 2·5 |
| | | $J_{6ax,7}$ = 12·7 | | | | |
| H-6ax | 7·34 (A) | $J_{6eq,7}$ = 3·6 | 7·43 (A) | $S_{6ax,7}$ = 11·8 | ? | |
| | | $J_{5,7}$ = 0·0 | | | | |
| eq | 7·83 (B) | $J_{7,8}$ = 7·1 | 7·92 (B) | $S_{6eq,7}$ = 3·8 | ? | |
| | | $J_{7,13}$ = 2·0 | | $S_{2,5}$ = 2·2 | | |
| | | $J_{7,13'}$ = 1·6 | | $S_{7,8}$ = 8·0 | | |
| | | | | $J_{7,13}$ = 2·7 | | |
| H-7 | 6·82 (Y) | $S_{2,5}$, $S_{2,6ax}$: 0·8, 0·7 | 6·80 (Y) | $J_{7,13'}$ = 2·1 | ? | |
| H-8 | 5·37 (X) | $J_{8,9ax}$ = 11·8 | 5·51 (X) | $S_{8,9ax}$ = 12·0 | 5·35 (X) | $S_{8,9ax}$ = 10·8 |
| | | $J_{8,9eq}$ = 4·9 | | $S_{8,9eq}$ = 4·0 | | $S_{8,9eq}$ = 2·1 |
| H-9ax | 7·29 (A) | $J_{9ax,9eq}$ = 12·9 | 7·37 (A) | $J_{9ax,eq}$ = 12·8 | 7·30 (A) | $J_{9ax,9eq}$ = 12·7 |
| eq | 7·54 (B) | $J_{7,8}$ = 7·1 | 7·71 (B) | $S_{7,8}$ = 8·0 | 7·65 (B) | $S_{7,8}$ = 6·8 |
| H-11 | | | — | | ? (X) | |
| H-13 | 3·74 (d) | $J_{7,13}$ = 2·0 | 3·76 (d) | $J_{7,13}$ = 2·7 | ~6·32 (A) | $S_{11,13}$ = 4·3 |
| | 4·31 (d) | $J_{7,13'}$ = 1·6 | 4·40 (d) | $J_{7,13'}$ = 2·1 | ~6·37 (B) | $S_{11,13'}$ = 3·6 |
| H-14 | 6·12 (A) | $J_{AB}$ = 7·2 | 5·99 (A) | $J_{AB}$ = 6·9 | 6·15 (A) | $J_{AB}$ = 6·9 |
| | 6·23 (B) | | 6·29 (B) | | 6·22 (B) | |
| H-15 | 8·44 (s, Me) | | 8·55 (s, Me) | | 8·43 (s, Me) | |
| Others | | | | | 6·64 (s, C-13—OMe) | |

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* Chemical shifts are measured on the τ-scale; coupling constants and splittings are given in Hz. Letters in brackets

DIHYDROGRIESENIN AND THEIR DERIVATIVES*

| IV | V | VIa | VIb |
|---|---|---|---|
| ? | ? | ~8·6 (c) | ? |
| 8·27 (c) | ? | ? | ? |
| - | · | 6·36 (c) | 6·33 (c) |
| 4·48 (broad d) $S_{5,6ax}$ = 8·7 | ? | ? | ? |
| ? | ? | ? | ? |
| ? | ? | ? | ? |
| ? | ? | 7·30 (c) | 7·33 (c) |
| 5·50 (X) $S_{8,9ax}$ = 11·7<br>$S_{8,9eq}$ = 4·1<br>7·39 (A) $J_{9ax,9eq}$ = 12·8<br>7·74 (B) $S_{7,8}$ = 7·3 | 5·66 (c) $S_{7,8}$ = 8·2<br>$S_{8,9ax}$ = 10·5<br>$S_{8,9eq}$ = 5·2<br>?<br>? | 5·39 (X) $S_{8,9ax}$ = 4·8<br>$S_{8,9eq}$ = 11·8<br>8·33 (B) $J_{9ax,9eq}$ = 13·5<br>7·48 (A) $S_{7,8}$ = 5·0<br>$J_{9ax,14}$ = 1·7 | 5·40 (X) $S_{8,9ax}$ = 11·7<br>$S_{8,9eq}$ = 4·8<br>8·26 (B) $J_{9ax,9eq}$ = 13·7<br>7·60 (A) $S_{7,8}$ = 4·5<br>$J_{9ax,14}$ = 1·0 |
| ? (X)<br>~6·35 (A) $S_{11,13}$ = 4·6<br>~6·39 (B) $S_{11,13'}$ = 3·6 | ? (X)<br>~6·35 (A)<br>~6·39 (B) | 7·13 (c) $S_{7,11}$ = 8·2<br>$J_{11,13}$ = 7·0<br>8·88 (d, Me) $J_{11,13}$ = 7·0<br>? | 7·15 (c) $S_{7,11}$ = 8·3<br>$J_{11,13}$ = 7·0<br>8·89 (d, Me) $J_{11,13}$ = 7·0<br>? |
| 6·02 (A)<br>6·36 (B) $J_{AB}$ = 6·9 | 6·07 (A)<br>6·43 (B) $J_{AB}$ = 7·0 | 6·00 (A) $J_{9ax,A}$ = 1·7<br>6·68 (B) $J_{AB}$ = 11·5 | 5·47 (A) $J_{9ax,A}$ = 1·0<br>5·99 (B) $J_{AB}$ = 12·0 |
| 8·55 (s, Me) | 8·56 (s, Me) | 8·85 (d, Me) $J_{4,15}$ = 6·0 | 8·89 (d, Me) $J_{4,15}$ = 5·6 |
| 6·65 (s, C-13—OMe) | 6·66 (s, C-13—OMe) | | 7·90 (s, C-14—OAc) |

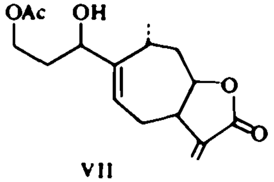
(e g (A)) indicate type of spin system; splittings (S) are quoted if no exact analysis has been performed.

Abbreviations: s = singlet; d = doublet; c = complex; S = splitting

The assignments have been done in analogy to griesenin and decoupling experiments have been performed to confirm the assignments of the alcohol VIa.

## DISCUSSION

*Conformation*. As griesenin has been extracted from the same plant as gafrinin (VII),[2,12] one would expect closely related configurations for these compounds. The stereochemistry of griesenin is therefore most conveniently discussed in relation to gafrinin.



VII

Comparison of the chemical shifts and coupling constants of the relevant protons given in Table 2 immediately reveals great similarities. The τ-values of the protons H-7 and H-8 suggest the same *cis*-fusion of the lactone and the cycloheptene rings and the coupling constant between these protons agrees with them being more or less eclipsed.

TABLE 2. COMPARISON OF NMR PARAMETERS FOR GRIESENIN AND GAFRININ

| | Griesenin | Gafrinin* |
|---|---|---|
| $\tau_{H\text{-}7}$ | 6·82 | 6·66 |
| $\tau_{H\text{-}8}$ | 5·37 | 5·37 |
| $J_{5,6}$ | 3·3, 9·1 | 6·8, 8·4 |
| $J_{6,7}$ | 3·6, 12·7 | 6·0, 11·0 |
| $J_{7,8}$ | 7·1 | 8·6 |
| $J_{8,9}$ | 4·9, 11·8 | 3·0, 11·0 |

* *J*-values for gafrinin are splittings

The two conformations discussed for the cycloheptene ring of gafrinin were the chair and the boat. The twist-boat, not considered explicitly for gafrinin,[5] is now thought to be the energetically favoured conformer of the cycloheptene ring because of less H—H repulsion forces.[13] This conformation is, however, definitely ruled out for gafrinin because of the H-9, H-10 couplings observed for some of its derivatives.

A quantitative comparison of the coupling constants in Table 2 is hampered by the fact that the values for gafrinin are only first-order splittings, which may deviate considerably from the true coupling constants. However, the qualitative agreement of the coupling constants between the H-7 and H-8 protons and their neighbouring methylene groups (C-6 and C-9, respectively) found for griesenin and gafrinin (one large and one small coupling for each $CH_2$—CH moiety) allows us to assign the same α-boat conformation to the cycloheptene ring of griesenin as for gafrinin. The other possible conformers (α-, β-chair, and β-boat) can be excluded as these have dihedral angles ($x$ H-6, H-7 and $x$ H-8, H-9) not conceivable with the observed coupling constants.[5] The ketal system attached to the cycloheptene ring in griesenin adds further rigidity and strain to the structure prohibiting pseudorotation into the twist-boat conformation and giving a possible explanation for the observed differences between coupling constants in griesenin and gafrinin.

As in gafrinin there is some distortion of the boat conformation which releases the strain of the γ-lactone ring and increases the very short C-14, H-6 axial distance. Estimates of the deviation from the ideally staggered boat conformation of the cycloheptene ring may be obtained from the magnitude of the coupling constants between the H-7 and H-8 protons. Their dihedral angle in an undistorted boat conformation would be 60°. The measured couplings indicate a much smaller angle (20°–30°) caused mainly by the strain in the lactone ring which tends to assume a planar conformation. The strain imposed on the cycloheptene ring by the ketal system apparently also enforces the eclipsing of the C-7—H and C-8—H bonds. The H-7, H-8 couplings are 7-8 Hz for all compounds except the alcohol VIa and its acetate VIb. Only in these compounds, where the strain in the lactone, the cycloheptene and the dihydropyrane rings has been reduced by saturating the double bonds and where the ketal ring has been opened, are the C-7—H and C-8—H bonds almost staggered as shown by the decrease in the H-7, H-8 couplings (4·5–5·0 Hz).

The $J_{6,7}$- and $J_{8,9}$-values are as expected for gauche and trans couplings (dihedral angles of 60° and 180°), although the larger gauche coupling between H-8 and H-9 suggests a dihedral angle slightly smaller than 60°. Vicinal H H couplings incorporating a sp²-hybridized carbon ($H{-}\overset{\parallel}{C}{-}C{-}H$) show an angle dependence similar to the Karplus relation[14] and the observation of a large coupling (9·1 Hz) between the pseudo-equatorial H-6 proton and the olefinic H-5 proton agrees with the small dihedral angle (10°–20°) found from models.

We have placed the C-10 substituent in an α-position in analogy to the C-14 methyl in gafrinin. This configuration is suggested on biogenetic grounds and supported by the following facts: The UV absorption ($\lambda_{max}$ = 237 mμ, ε 17,900) agrees perfectly with a coplanar *trans*-diene system.[15] A ketal system with a β-C-14 group would twist the double bonds relative to each other. On opening the ketal system we observe a pronounced shift in the NMR spectrum of the pseudo-axial H-9 proton (τ = 7·29 → 8·33), while there is hardly any effect on the other H-9 proton. This could not be explained if the C-14 group was trans to the pseudo-axial H-9 proton as in a structure with a β-methylene.

The coupling constants observed for dihydrogriesenin indicate that no major conformational changes take place on saturating the 2,3-double bond. Models show that a boat conformation of the tetrahydropyran ring imposes less strain on the cycloheptene ring than a chair, but we have no further evidence to support this suggestion.

*Coupling constants and chemical shifts.* The presence of a *trans*-diene system in griesenin has been established from IR and UV data.[1] The assignment of the NMR signals due to the olefinic protons on C-2 and C-3 posed some problems although they were readily identified by their typical *cis*-coupling[16, 17] of 9·4 Hz. Their chemical shifts were rather similar and from other values on *trans*-dienes one would have expected the resonance of H-2 to occur at lower field.[18, 19] However, long-range splittings of 0·7 and 0·8 Hz observed in the doublet centred at $\tau = 4{\cdot}17$ were shown by decoupling to be due to interactions with the proton H-5 and the pseudo-axial proton on C-6, leading to the assignment given in Table 1.

The allylic couplings between the protons of the exocyclic methylene group and H-7 are smaller than in gafrinin supporting the previous conclusion that the formation of the ketal ring affects the conformation of the lactone ring. The *cisoid* coupling remains the smaller as in gafrinin.

The C-14 methylene protons have $\tau$-values close to those reported for protons in a similar environment (2-alkyl-1,3-dioxolan, $\tau = 6{\cdot}12$[20]) and their geminal coupling (6·9–7·2 Hz) agrees well with couplings between $\alpha$-protons in tetrahydrofuran derivatives ($-6{\cdot}7$ to $-9{\cdot}9$ Hz[21]). When the ketal ring is opened as in the alcohol VIa, we measure the chemical shifts ($\tau = 6{\cdot}00$ and 6·68) and coupling constant ($J = 11{\cdot}5$ Hz) expected for a $CH_2OH$-group. The large chemical shift difference between the H-14 protons is evidence for a preferred conformation of the $CH_2OH$-group as is the relatively large (1·7 Hz) long-range coupling between one of the methylene protons and the pseudo-axial proton on C-9.

## EXPERIMENTAL

The spectra were obtained from dilute $CDCl_3$ solns on Varian A-60 and HA-100 spectrometers with TMS as internal reference at probe temps of 38 and 32, respectively. Chemical shifts, quoted as $\tau$-values, are estimated to be accurate to ±0·01 ppm coupling constants to ±0·1 Hz. Decoupling experiments were performed in the frequency sweep mode of the Varian HA-100 spectrometer using a Hewlett Packard 200 CD audio-oscillator and a Hewlett-Packard 5521A electronic counter

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