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# A STUDY OF THE STEROECHEMISTRY OF TERPENOID COUMARINS OF THE IRESANE SERIES BY PMR SPECTROSCOPY WITH ADDITIONS OF $Eu(DPM)_3$

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Four isomeric coumarins containing a terpenoid substituent of the iresane type in position 7 have been isolated from various representatives of the genera *Ferula* and *Colladonia*. The structure and absolute configuration of one of them [farnesiferol A (I)] were established mainly by chemical methods together with the ORD method [1]. Caglioti et al. [1] did not obtain unambiguous proofs for the configuration of $C_1'$, but on the basis of indirect evidence they proposed the β-axial orientation as the most probable for the $C_1'$—$CH_2$ group. Scott et al., [2], by analogy with other diterpenoids, put forward the hypothesis of the equatorial orientation of the $C_1'$—$CH_2$ group in farnesiferol A.

Another coumarin, gummosin (II), is an epimer of farnesiferol A at $C_6'$ and differs from it only by the orientation of the hydroxy group, which is axial in gummosin and equatorial in farnesiferol A [3].

Again, no proof of the configurations at $C_1'$ has been obtained for the following pair of epimers at $C_6'$, badrakemin (III) [4, 5] and colladonin* (IV) [6]. In addition, the nature of the linkage of the rings in the decalin nucleus has not been determined for these compounds. As well as this, on the basis of the PMR spectrum of badrakemin and a comparison of them with the corresponding characteristics of gummosin, the equatorial orientation of the $C_1'$—$CH_2$ group in it has been suggested.

Thus, the configuration at $C_1'$ has not been established reliably for even one of the compounds mentioned.

We set ourselves the task of studying the relative configurations of these compounds by the PMR method using europium tris(dipivaloylmethanate) as paramagnetic shift reagent (PSR).

Below we give the PMR spectra of all four isomers (Figs. 1 and 2) and the chemical shifts (CSs) and spin—spin coupling constants of the main signals (Table 1). It can be seen from Figs. 1 and 2 and Table 1 that the epimeric pairs at $C_6'$ — farnesiferol A and gummosin, on the one hand, and colladonin and badrakemin, on the other hand — differ, in the first place, as the positions of the signals of the exocyclic methylene group (the CS between the two signals for the first pair is 0.10 ppm and for the second pair 0.37 ppm), and, in the second place, by the shape of the signal from the $C_1'$—$CH_2$ grouping; in farnesiferol A and gummosin the latter appears in the form of two one-proton quartets with a distance of one from the other of 0.29-0.31 ppm, and in the pair colladonin—badrakemin they appear in the form of a two-proton multiplet.

Colladonin and badrakemin may differ from farnesiferol A and gummosin, respectively, either by the nature of the linkage of the decalin ring system or by the orientation of the methylene group at $C_1'$, or by both these characteristics.

*Colladonin is identical with isobadrakemin, obtained from badrakemin [4].

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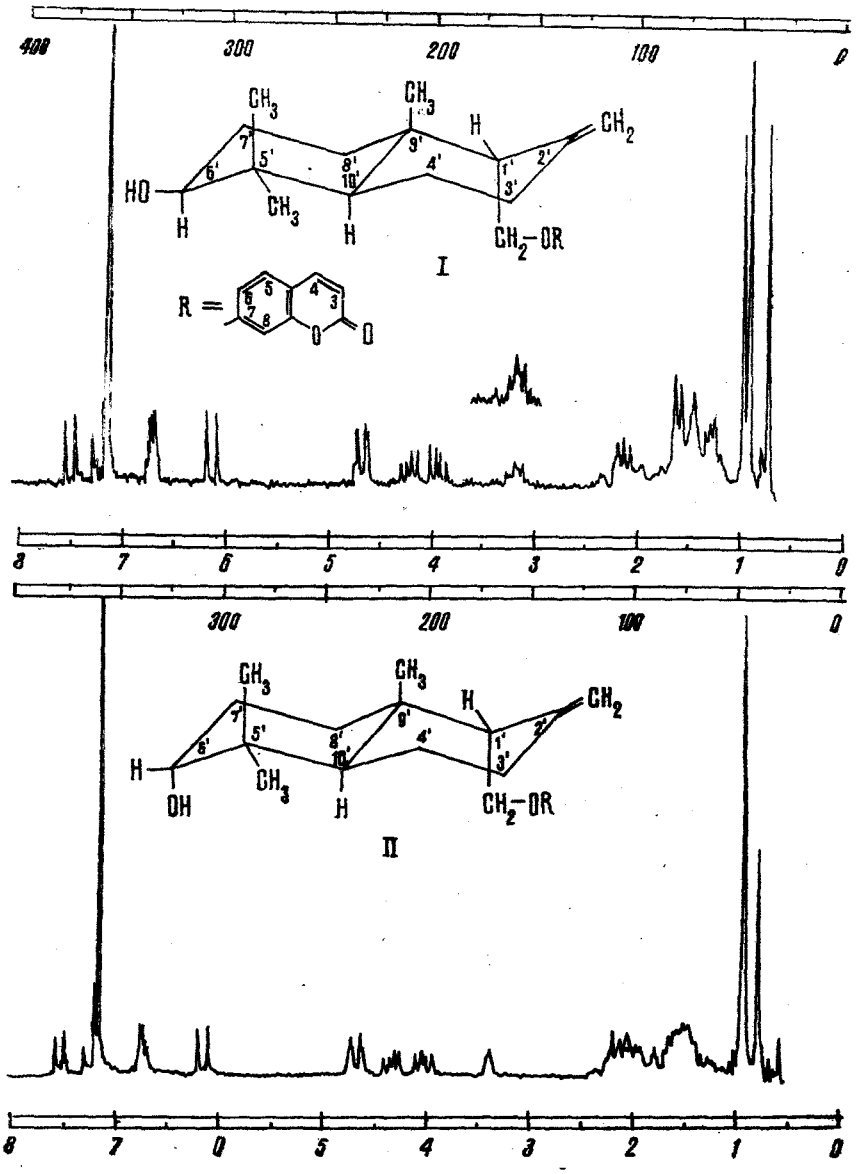


Fig. 1. PMR spectra of farnesiferol A (I) and gummosin (II).

It is known that in cis-decalin derivatives the conversion of the ring is possible, and in decalin itself it becomes fairly inhibited only at −117°C [7]. The practical coincidence of the values of the spin–spin coupling constants of the proton at $C_6'$ for farnesiferol A and colladonin, and also for gummosin and badrakemin (see Table 1), shows the absence of conversion or of a predominant shift of the equilibrium in the direction of one of the conformers. The equality of the CSs of the protons of the gem-dimethyl grouping in the spectra of the pairs farnesiferol A–colladonin and gummosin–badrakemin, in each of which the first compound contains a trans-decalin nucleus, permits the conclusion of the trans linkage of the rings in the terpenoid residues of colladonin and badrakemin.

Thus, colladonin and badrakemin differ from farnesiferol A and gummosin only by their configuration at $C_1'$.

The PMR spectra (see Figs. 1 and 2) show the presence of stereochemical differences but do not provide the possibility of demonstrating sufficiently strictly in which of the two pairs the methylene group at $C_1'$ is equatorial and in which it is axial. Answering this question proved to be possible by using the PSR method in PMR spectroscopy.

The use of the PSR method for solving structural and stereochemical problems is based on the dependence of the magnitude of the observed shifts of the signals on the distance from the corresponding protons to the metal ion, or more roughly, to the center of complex-formation which is, as a rule, the most basic heteroatom [8-11]. Such a relationship exists

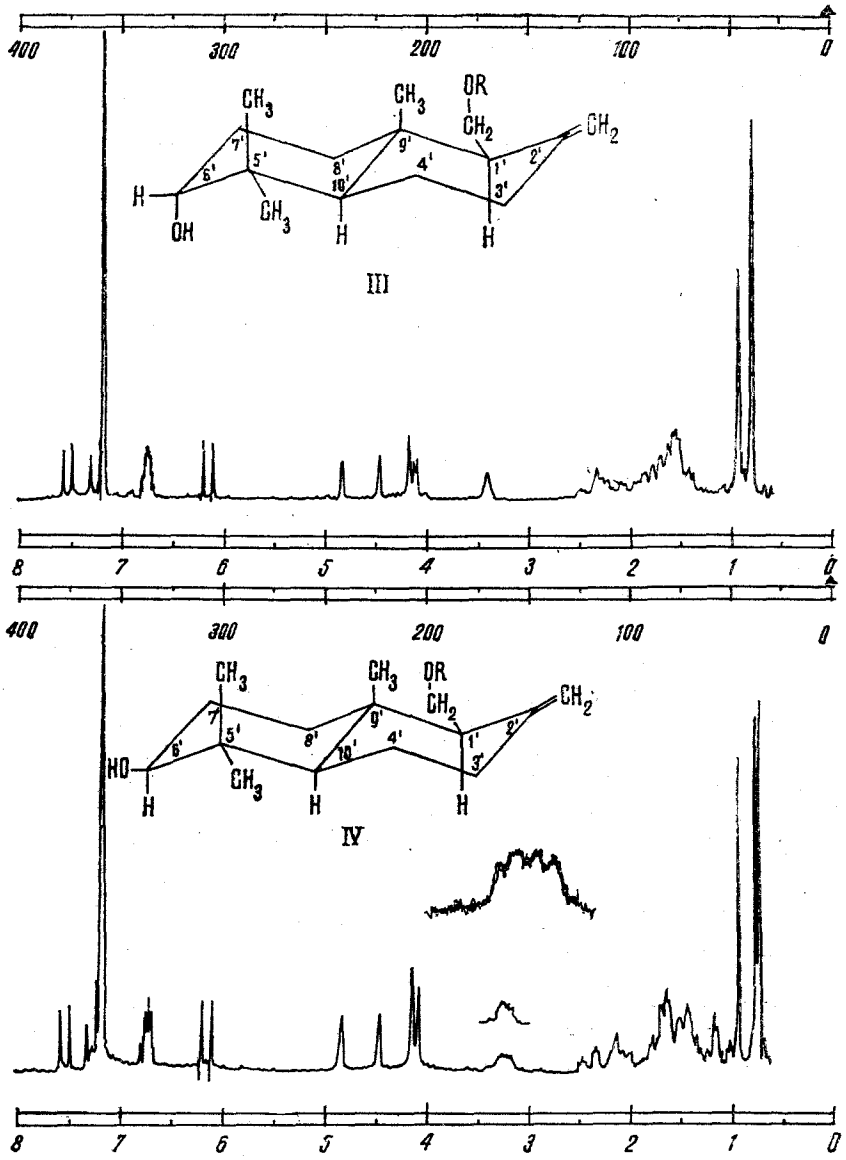


Fig. 2. PMR spectra of badrakemin (III) and colladonin (IV).

only where the change in the CSs of the signals takes place mainly as a result of the so-called pseudocontact interaction. It has been shown that this type of interaction is predominant when complexes of the lanthanides are used as PSRs [10].

The spectra of compounds (I-IV) were obtained in $CDCl_3$ at various molar ratios of reagent to substance. From the relation $\Delta\delta = \delta_{Eu(DPM)_3} - \delta_{CDCl_3}$ we determined the change in the CSs of the protons of the following groups: $C_1'-CH_2$, $C=CH_2$, $C_5'-CH_3^e$, $C_5'-CH_3^a$, and $C_9'-CH_3$. In Fig. 3, using gummosin as an example, the dependence of $\Delta\delta$ on the molar ratio of reagent to substance is given. The "reduced shift" ($\Delta$Eu), which represents the value of $\Delta\delta$ at a ratio of reagent to substance of 1 is obtained by extrapolation.

We found the values of $\Delta$Eu of the protons of the groups mentioned above for the other compounds studied in a similar manner (Table 2).

Then, for each compound, on Dreiding models we measured the distances from the oxygen atoms of the hydroxy group to the protons given above.* In the case of methyl groups, we measured the distance to the center of gravity of the three hydrogen atoms. The trans linkage of the rings and the orientation of the hydroxy group unambiguously determined from

*According to Hart and Love [12], the hydroxyl group is the most active center of complex formation; the paramagnetic shift of the signals of the protons of the sesquiterpenes as the result of complex formation at the carbonyl of the $\alpha$-pyrone ring is apparently insignificant.

TABLE 1. Parameters of the PMR Spectra of Farnesiferol A, Gummosin, Badrakemin, and Colladonin*

| Proton | δ, ppm; multiplicity, J, Hz | | | |
|---|---|---|---|---|
| | farnesiferol A | gummosin | badrakemin | colladonin |
| $C_{5'}-CH_3^a$ | 0,98; s | 0,79; s | 0,78; s | 0,96; s |
| $C_{5'}-CH_3^e$ | 0,75; s | 0,9 ; s | 0,93; s | 0,78; s |
| $C_{9'}-CH_3$ | 0,92; s | 0,92; s | 0,78; s | 0,74; s |
| $C=CH_2$ | 4,65; m, $W_{\frac{1}{2}}=5,0$ | 4,64;m; $W_{\frac{1}{2}}=4,0$ | 4,52; ur , $W_{\frac{1}{2}}=3,5$ | 4,48; ur, $W_{\frac{1}{2}}=4,0$ |
| | 4,75; m, $W_{\frac{1}{2}}=5,0$ | 4,74; m, $W_{\frac{1}{2}}=4,0$ | 4,89; ur, $W_{\frac{1}{2}}=3,5$ | 4,85; ur, $W_{\frac{1}{2}}=4,0$ |
| $C_{1'}-CH_2-O$ | 3,95; a;10,2; 5,9<br>4,24; q; 10,2; 6,2 | 4,03; q; 10,0; 5,5<br>4,34; q; 10,0; 6,6 | 4,20 †; м | 4,13 †; m |
| $C_{6'}-H$ | 3,20; t , $\Sigma J=15$ | 3,40; ur, $W_{\frac{1}{2}}=7$ | 3,03,45;ur ; $W_{\frac{1}{2}}=7,0$ | 3,25; q ; 9,5; 5,0 |
| $C_3-H$ | 6,17; d; 9,5 | 6,16; d 9,5 | 6,22; d; 9,5 | 6,18; d; 9,5 |
| $C_4-H$ | 7,54; d; 9,5 | 7,54; d; 9,5 | 7,60; d ; 9,5 | 7,55; d; 9,5 |
| $C_5-H$ | 7,28; d; 8,8 | 7,27; d 8,8 | 7,33; d ; 9,0 | 7,29; d ; 8,5 |
| $C_8-H$ | 6,73; q; 8,8; 2,2 | 6,75; q ; 8,8; 2,2 | 6,80; q ; 9,0; 2,3 | 6,75; q; 8,5; 2,0 |
| $C_8-H$ | 6,73; d; 2,2 | 6,75; d ; 2,2 | 6,80; d ; 2,3 | 6,75; d; 2,0 |

*s) Singlet; d) doublet; t) triplet; q) quartet; m) multiplet; ur) unresolved or weakly resolved signal appearing in the form of a singlet; $W_{1/2}$ - half-width of the signal. The assignments of the signals of the methyl groups were made with a consideration of the features of the spectra in the presence of $Eu(DPM)_3$.
†Center of a multiplet.

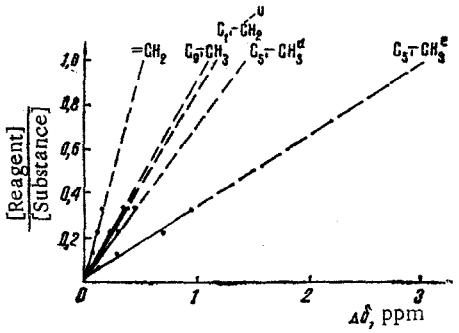


Fig. 3. Dependence of the change in the CS (Δδ) of a series of protons of gummosin on the reagent/substance ratio.

the spin—spin coupling constants of the proton geminal to it were assumed. Thus, for each compound two variants of the configuration remained — with the axial and with the equatorial position of the $C_1'-CH_2$ group.

Figure 4 gives the dependence of log ΔEu on log r, where r is the distance in Å from the corresponding protons to the oxygen atom of the OH group for the two variants of each of the compounds investigated. The tangent of the angle of slope of the straight line obtained by treating the experimental results by the method of least squares is −1.95 to −2.10 in all cases, which is close to the value given by Demarco et al. [9].

It can be seen from Fig. 4 that for all three compounds it is possible to make an unambiguous choice from the two alternative variants of the orientation of the $C_1'-CH_2$ group, since the point corresponding to the other variant lies to one side of the straight line. Consequently, the $C_1'-CH_2$ group in farnesiferol A and gummosin is axial, and in colladonin and badrakemin it is equatorial. Therefore, farnesiferol A and gummosin are represented by formulas (I) and (II) (see Fig. 1) and badrakemin and colladonin by formulas (III) and (IV), or their mirror images (see Fig. 2).

TABLE 2. "Reduced Shifts" of a Series of Protons of Compounds (I)-(IV)

| Proton | ΔEu, ppm | | | |
|---|---|---|---|---|
| | farnesiferol A | gummosin | colladonin | badrakemin |
| $C_{1'}-CH_2-O$ | 0,98 | 1,22 | 0,72 | 1,55 |
| $C=CH_2$ | 0,78 | 0,54 | 0,60 | 1,12 |
| $C_{5'}-CH_3^a$ | 5,84 | 1,48 | 4,16 | 3,77 |
| $C_{5'}-CH_3^e$ | 6,46 | 3,14 | 4,70 | 7,10 |
| $C_{9'}-CH_3$ | 2,56 | 1,16 | 1,94 | 2,65 |

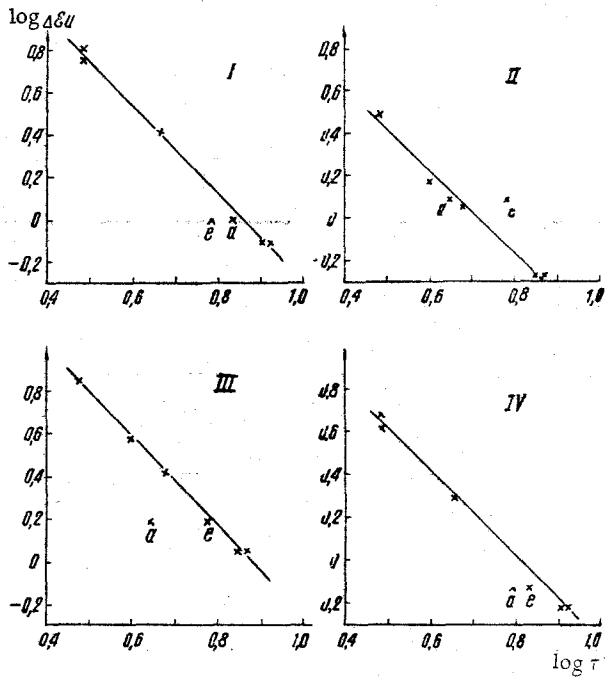


Fig. 4. Dependence of log ΔEu on log r for a series of protons in compounds (I)-(IV): *a* and e are the points corresponding to the axial and equatorial orientations of the $C_1'-CH_2$ group.

A number of papers [13-15] has been published recently in which, on the basis of a comparison of the PMR spectra of (I-IV) erroneous conclusions have been drawn concerning the equatorial orientation of the $C_1'-CH_2$ group in gummosin and its axial orientation in badrakemin, and on the identity of colladonin with farnesiferol A. It can be seen from a consideration of the parameters and the reproduction of the PMR spectrum of "farnesiferol A" given in two or these papers [13, 15] that Saidkhodzhaev et al. [13-15] took colladonin as farnesiferol A. This was also the cause of a number of erroneous conclusions concerning the stereochemistry of the terpenoid coumarins and incorrect deductions about the connection between the spectral characteristics and configurations of the molecules of compounds of this series.

A simple comparison of the melting points of the series of compounds given in the literature also shows the incorrectness of the conclusions given [13, 14]. Thus, the oxidation of farnesiferol A [1] and gummosin [3] gave a common ketone with mp 132-134°C; the oxidation of badrakemin and colladonin also gave a common ketone — badrakemone — with mp 185-186°C [4, 6]. If colladonin were identical with farnesiferol A, as is stated by Saidkhodzhaev et al. [13, 14], its oxidation should give a ketone with mp 132-134°C and not one with mp 185-196°C [6].

The compound described in [15] under the name of "mogoltadin" is farnesiferol A, as follows from a comparison of its PMR spectrum with that of farnesiferol A.

## EXPERIMENTAL

The spectra were obtained on an HA-100D/100 MHz instrument at 20°C using $CdCl_3$ as the solvent; 0 — HMDS.

The melting point of the farnesiferol A was 155°C, of the gummosin 175-176°C, of the badrakemin 198-199°C, and of the colladonin 158-159°C.

## SUMMARY

A study of the PMR spectra of farnesiferol A, gummosin, badrakemin, and colladonin in the presence of the paramagnetic shift reagent $Eu(DPM)_3$ has established the configurations at $C_1$' in the molecules of these compounds and the trans linkage of the decalin ring in the badrakemin and colladonin molecules. Taking previously published work into account [1], the absolute configuration of the first two compounds and the relative configuration of badrakemin and colladonin are now known.

2. The conclusions concerning the stereochemistry of these compounds and the laws connecting the spectra and configurations of the molecules made by Saidkhodzhaev et al. [13, 14] are erroneous.

3. The compound described in [15] under the name "mogoltadin" is farnesiferol A.

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