UNUSUAL CYCLIZATION IN THE 11-HYDROXY-1βH,5βH,6βH,7αH-GUAIAN-6,12-OLIDE SERIES*

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Derivatives of the keto triester *II*, particularly the ether *VI*, were investigated by ^{1}H-NMR and CD spectroscopy. Formation of the ether *VI* and comparison of its parameters with those of other described compounds prove that the originally suggested steric structure of acetylisomontanolide (*VII*) is correct.

Recently we assigned constitution and relative as well as absolute configuration to a series of native lactones, related to montanolide[1,2] (*I*), using chemical and spectroscopic evidence. This evidence indicated that these lactones, isolated hitherto only from species of the *Laserpitieae* tribe (*Umbelliferae* family), are guaian-6,12-olides with an unusual configurational sequence 1βH,5βH,6αH,7αH, analogous to that of pseudoguaian-6,12-olides. Now, we succeeded in obtaining further evidence of this stereochemistry, unusual in the guaianolide series.

We tried to correlate the mentioned compounds with known guaianolides *via* products of elimination of the hydroxyl at $C_{(11)}$ which could be compounds either with tetrasubstituted double bond between $C_{(7)}$ and $C_{(11)}$ or with an exo-methylene double bond between $C_{(11)}$ and $C_{(13)}$. As starting compounds we chose 3-oxo derivatives derived from the keto triester *II* in order to be able to check partly the stereochemistry of the prepared compounds by CD spectra. Partial saponification of the keto triester *II* afforded two products. One was the diester *III* with free hydroxyl group at $C_{(11)}$, as proved by the TAI method[3]: *in situ* acylation with trichloroacetyl isocyanate (TAI) gave the trichloroacetylcarbamoyl derivative *IV*; the small acylation shift of the tertiary methyl signal $\Delta\delta H_{(13)} = 0{\cdot}1$ Hz indicated an α-position of the hydroxyl relative to the oxo group of the γ-lactone ring[3]. The second product was the mono ester *V* with free hydroxyl groups at $C_{(10)}$ and $C_{(11)}$. As proved by the ^{1}H-NMR and CD data, the saponification of the triester *II* to *III* or to *V* was not accompanied by any stereochemical change, the configuration of the methyl group at $C_{(4)}$ being retained ($J_{4.15} \approx 7{\cdot}6-7{\cdot}7$ Hz in all cases); there was also no configurational change of the five-membered ring with the keto group (CD spectra exhibit

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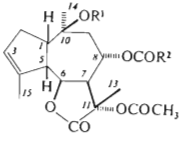
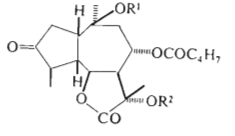
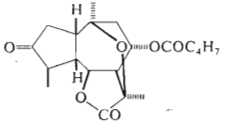
in the 300 nm region maxima of $\Delta\varepsilon$ +1·48 to +2·54). Attempted elimination of the hydroxyl in position 11 did not lead to any of the expected derivatives. The only defined elimination product was obtained by treatment of the compound *V* with phosphorous oxychloride in pyridine. This product contained no hydroxyl, as shown





I; $R^1 = H$; $R^2 = CH{=}C(CH_3)_2$
VII: $R^1 = COCH_3$; $R^2 = C(CH_3){=}CHCH_3$

II: $R^1 = R^2 = COCH_3$
III: $R^1 = COCH_3$; $R^2 = H$
IV: $R^1 = COCH_3$; $R^2 = CONHCOCCl_3$
V: $R^1, R^2 = H$



VI

both by the IR and ^{1}H-NMR spectra. As follows from the mass spectrum (MS^+: 362), IR spectrum (γ-lactone: 1784 cm^{-1}, conjugated ester group: 1722 and 1647 cm^{-1}, oxo group in the five-membered ring; 1742 cm^{-1}) and from a detailed analysis of the ^{1}H-NMR spectrum (Table I and II), the product is the 10,11-ether *VI*. Formation of this compound is quite plausible, considering the suggested stereochemistry of the chiral centers in acetylisomontanolide (*VII*) and thus also in the starting dihydroxy ester *V*. As shown by analysis on Dreiding models, for the given set of chirality centers the ether can be formed only in a system of the 1βH,5βH,6αH,7α-H--guaian-6,12-olide configuration, proposed previously for acetylisomontanolide (*VII*). The *cis*-lactone arrangement at $C_{(6)}$ and $C_{(7)}$ is particularly important because, for steric reasons, the *trans*-lactone cannot be cyclized to give the ether in question. The configuration assigned to the hydroxyl groups (β at $C_{(10)}$ and α at $C_{(11)}$ in the dihydroxy ester *V*) requires an S_N2 reaction with inversion at $C_{(11)}$. Anyway, the observed cyclization implies in principle α,β or β,α configuration of the hydroxyl groups at $C_{(10)}$ and $C_{(11)}$ and supports the *anti*-configuration assignment previously made on the basis of TAI acylation shifts. These arguments can now be combined with the observed acylation shift (TAI method[3], TAC = $CONHCOCCl_3$), $\Delta^{(11)}\delta H_{(7)}$ (TAC) = $\delta H_{(7)}$ (*III*) − $\delta H_{(7)}$ (*IV*) = +0·75 ppm, which indicates a "*syn*" relation of $H_{(7)}$ and $C_{(11)}$—OR and thus α-configuration of the $C_{(11)}$—OR

bond. The conformational "purity" of this shift (conditioned by the identity of conformations of R in R—OH and R—OTAC) is obvious from the invariance of the coupling constants in compounds *III* and *V* (Table II).

As follows from models, the ether *VI* can be expected to exist in two conformational types: one with a "positive" half-chair conformation of the five-membered homocycle (3-oxocyclopentane moiety) and $C_{5\beta}$-boat-like conformation of the seven-membered heterocycle, involving the $C_{(10)}$—O—$C_{(11)}$ oxygen atom, and other with a "negative" half-chair conformation of the five-membered homocycle and $C_{5\alpha}$-chair-like conformation of the seven-membered heterocycle (terms $C_{n\alpha}$ or $C_{n\beta}$ denote configuration of the atom in symmetry plane of the regular conformation[5]). The first type can *a priori* be considered to be less advantageous because of potential steric interactions between $H_2C_{(2)}$ and the α-substituent at $C_{(8)}$.

As shown by CD and ^{1}H-NMR spectra, the compound indeed exists in the latter conformation, depicted in Fig. 1. Whereas CD spectra of the starting ketone *II*, as well as of other 3-oxo derivatives, exhibited a characteristic band of carbonyl group at about 300 nm ($\Delta\varepsilon$ +1·5 to +2·5), in CD spectrum of the ether *VI* this band was located at 296 nm, its $\Delta\varepsilon$ being −2·1. This inversion of the Cotton effect

TABLE I

Characteristic ^{1}H-NMR Spectral Parameters of Compounds *III*—*VI*

Compound	$H_{(5)}$	$H_{(6)}$	$H_{(7)}$	$H_{(8)}$	$H_{(9)}$	$H_{(9')}$	$H_{(13)}$	$H_{(14)}$	$H_{(15)}$
III	2·55	4·54	3·18	5·76	2·67	2·20	1·58	1·55	1·22 d
IV	—	4·88	3·93	5·76	2·75	2·20	1·66	1·55	1·21
V	—	4·51	3·23	5·68	—	—	1·49	1·25	1·17
VI[a]	2·46	4·89	2·87	5·46	2·37	1·60	1·52	1·24	1·16

[a] $H_{(1)}$: 2·65 m, $H_{(2)}$: 2·59 m, $H_{(2')}$: 2·25 dd, $H_{(4)}$: 2·89 ddq.

TABLE II

Splitting Constants of Compounds *III*—*VI*

Compound	$J_{5,6}$	$J_{6,7}$	$J_{7,8}$	$J_{8,9}$	$J_{8,9'}$	$J_{4,15}$	$J_{9,9'}$
III	12·1	9·7	10	10·3	1·3	7·7	15
IV	12·3	10·3	10·5	10·5	<1·5	7·6	15
V	13	10	10	—	—	7·7	—
VI[a]	1·8	7·2	5·7	11·3	4·6	6·7	16

[a] $J_{2',4} = 1{\cdot}8$, $J_{2,2'} = 17{\cdot}5$, $J_{4,5} = 13{\cdot}5$, $J_{5,1} = 7{\cdot}7$, $J_{1,9} = 1{\cdot}5$

is in complete agreement with the assumed positive half-chair conformation of the cyclopentanone grouping in compounds *II* – *V* and negative half-chair conformation in the ether *VI* (Fig. 2). The negative half-chair conformation of the five-membered

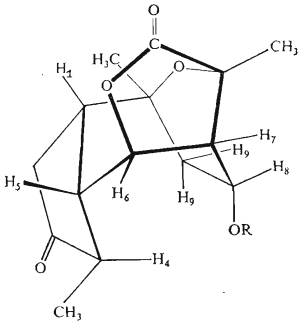


FIG. 1
Molecular Conformation of Ether *VI*

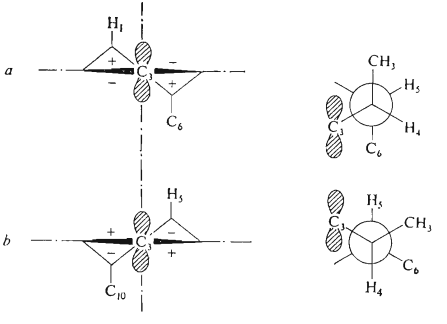


FIG. 2

Conformational Alternatives of the Cyclopentanone System in 3-Oxo-1βH,4αH,5βH--guaianolides and Newman Projections of the $C_{(4)}$—$C_{(5)}$ Fragment

a) Positive half-chair conformation of the ketones *II*—*V* (300 nm, $\Delta\varepsilon$ +1·5 to +2·5); *b*) negative half-chair conformation of the ether *VI* (296 nm, $\Delta\varepsilon$ —2·1).

ring with β-configuration of the methyl group at $C_{(4)}$ is indicated also by the magnitude of the vicinal coupling constant $J_{4,5}$ (13·5 Hz) which proves unequivocally an antiperiplanar arrangement of the atoms $H_{(4)}$ and $H_{(5)}$. The conformationally significant change of the coupling constant $J_{4,15}$ from about 7·7 Hz in the ketones *II* – *V* to 6·7 Hz in the ether *VI* is interesting in this context. As already mentioned elsewhere[1], the magnitude of $J_{4,15}$ in the ketones *II* – *V* violated apparently the rule[5,6] stating that $J_{4,15}(H_{(5)}, CH_3\ syn) < J_{4,15}(H_{(5)}, CH_3\ anti)$ because the high value of $J_{4,15}$ (7·7 Hz) indicated in the guanianolide series rather an *anti*-relation between $H_{(5)}$ and CH_3—$C_{(4)}$, contradicting thus the postulated configuration of the center $C_{(4)}$. This discrepancy was ascribed[1] to the invalidity of the mentioned rule in the case of the 3-oxo derivative, caused by the presence of the keto group in α-position relative to the secondary methyl group. Now, it is obvious that the rule[6] J_{H,CH_3} (CH_3,R *syn*) > J_{H,CH_3} (CH_3,R *anti*) (R being a perturbing group), of which the above-mentioned rule for guaianolides is a special case, is valid also in these cases. The reason of the mentioned discrepancy is that the dominating perturbing group is not the $C_{(6)}$—OR group but the carbonyl π-electron pair. For 3-oxoguaianolides (Fig. 2) $J_{4,15}$ (CH_3 equatorial) is smaller than $J_{4,15}$ (CH_3 axial), irrespective of the configuration of the center $C_{(5)}$. In the 3-deoxy derivatives, the grouping $C_{(6)}$—OR plays again the dominant role and the value of $J_{4,15}$ then depends on the configuration at $C_{(5)}$ (ref.[5]).

For the considered conformation of the ether *VI* there is also a very good overall accord of all vicinal coupling constants with the corresponding values of torsion angles in the conformation depicted in Fig. 1.

The formation of ether *VI* confirms thus the unusual steric structure of acetylisomontanolide (*VII*) and related compounds, suggested in the previous paper[1].

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Column chromatography was performed on silica gel according to Pitra and Štěrba (30—60 μm; deactivated by addition of 11% water), thin-layer chromatography was carried out on silica gel according to Stahl (Merck). ^{1}H-NMR spectra were measured in deuteriochloroform on a Varian HA 100 instrument with tetramethylsilane as internal standard. Mass spectra were taken on an AEI 902 spectrograph. Optical rotation was determined on a Perkin–Elmer 141 polarimeter in chloroform. CD spectra were taken on a Roussel/Jouan CD 185 dichrograph in methanol.

Hydroxy Diester *III*

A solution of sodium methoxide in methanol (1·1 ml; concentration 1 mol l^{-1}) was added to a solution of the keto triester *II* (465 mg) in methanol (5 ml), the mixture was set aside for 24 h at room temperature and taken down *in vacuo*. The residue was dissolved in water (50 ml), acidified with acetic acid and taken up in chloroform. The combined chloroform extracts were washed with a saturated solution of sodium hydrogen carbonate and with water, dried over sodium sulfate and the solvent evaporated *in vacuo*, affording the product *III* (350 mg; 83%), m.p. 185 to

187°C, $[\alpha]_D^{20}$ +8·8° (*c* 0·28). IR spectrum (cm^{-1}): 3475, 3570 (hydroxyl), 1777 (γ-lactone), 1743, 1250 (acetate), 1720 (shoulder, conjugated ester), 1651 (double bond). Mass spectrum (*m/e*): 404 (M—18), 262 (M—60—100), 83 ($C_4H_7CO^+$), 55 ($C_4H_7^+$). CD spectrum: 300 nm, $\Delta\varepsilon$ +2·16; 252 nm, $\Delta\varepsilon$ —0·16. For $C_{22}H_{30}O_8$ (422·5) calculated: 62·45% C, 7·16% H, 0·24% H act.; found: 62·49% C, 7·34% H, 0·27% H act.

Dihydroxy Monoester *V*

A solution of sodium methoxide in methanol (2·5 ml; concentration 1 mol l^{-1}) was added to a solution of the keto triester *II* (465 mg) in methanol (5 ml) and the mixture was set aside for 48 h at room temperature. The solvent was evaporated *in vacuo* and the residue worked up analogously as described in the preceding experiment, affording the product *V* (297 mg; 78% yield), m.p. 202—204°C, $[\alpha]_D^{20}$ +60·2° (*c* 0·24). IR spectrum (KBr; cm^{-1}): 3390, 3510 (hydroxyl), 1762 (γ-lactone), 1710 (ketone in a five-membered ring), 1680 (conjugated ester), 1640 (double bond). Mass spectrum (*m/e*): 362 (M—18), 291 ($C_{17}H_{23}O_4$), 244 (M—100—18—18), 191 ($C_{12}H_{15}O_2$), 100 (C_4H_7COOH), 83 ($C_4H_7CO^+$), 55 ($C_4H_7^+$). CD spectrum: 301 nm, $\Delta\varepsilon$ +2·51; 252 nm, $\Delta\varepsilon$ —0·16. For $C_{20}H_{28}O_7$ (380·4) calculated: 63·14% C, 7·42% H, 0·53% H act.; found: 63·32% C, 7·53% H, 0·62% H act.

Ether *VI*

Phosphorus oxychloride (60 mg) was added to a solution of the dihydroxy monoester *V* (100 mg) in pyridine (5 ml). After stirring for 10 min at room temperature, the mixture was decomposed with ice, diluted with water and extracted with ethyl acetate. The combined organic layers were worked up, affording 87 mg of crude product which was purified by chromatography on a column of silica gel (10 g) using benzene–ethyl acetate (2 : 1) as eluant. Yield 32 mg (34%) of compound *VI*, m.p. 173—176°C. IR spectrum (cm^{-1}): 1784 (γ-lactone), 1742 (ketone in a five-membered ring), 1722 (conjugated ester), 1647 (double bond). Mass spectrum (*m/e*): 362 (M), 262 (M—100), 100 (C_4H_7COOH), 83 ($C_4H_7CO^+$), 55 ($C_4H_7^+$). CD spectrum: 296 nm, $\Delta\varepsilon$ —2·01; 255 nm, $\Delta\varepsilon$ —0·42 (min). For $C_{20}H_{26}O_6$ (362·4) calculated: 66·28% C, 7·23% H; found: 66·12% C, 7·44% H.

The elemental analyses were performed in the Analytical Department of our Institute (Dr J. Horáček, Head) by Mrs A. Froňková, Mr V. Štěrba and Dr V. Pechanec. IR spectra were taken by Mrs K. Matoušková and Mr P. Formánek under supervision of Dr S. Vašíčková (who interpreted the IR as well as the CD spectra). Mass spectra were measured and interpreted by Dr L. Dolejš. Optical rotation measurements were carried out by Mrs Z. Ledvinová. Our thanks are due all these mentioned.

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