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CONFORMATION OF CYCLOHEXENONES

APPLICATION OF LONG-RANGE COUPLING TO CONFORMATIONAL ANALYSIS*

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Abstract—NMR spectra of several α,β-unsaturated cyclohexenone derivatives were investigated. Long-range coupling between β-hydrogen and a hydrogen which is separated from the β-hydrogen by four bonds is observed in magnitude of 1–2 Hz for some compounds. By the application of W-rule to this result and by analysis of vicinal coupling, the conformations of cyclohexenone rings of the above compounds were determined as follows: decalen-1-on-3 derivatives which, show the long-range coupling, exist in *cis* juncture and non-steroidal conformation. Results obtained were further confirmed by conformational analysis and by consideration of their ORD and CD spectra.

RECENTLY, long-range coupling through four or more bonds has been popular in the literatures.[1] We have found an example of such a long-range coupling in the natural products which contain an α.β-unsaturated carbonyl group and conjugated double bond system.[2,3] This result compels us to make another extended investigation about the angular dependency of the long-range coupling since a theoretical approach to this problem was formulated by Barfield.[4]

Signals of β-hydrogens of α.β-unsaturated carbonyl compounds appear at positions rather isolated from those of other types of hydrogens. Thus, signals of β-hydrogens of these types compounds are easily distinguished from other signals. Taking this into account, we choose several α.β-unsaturated cyclohexenone derivatives and occidentalol in order to determine their conformations by means of β-hydrogen long-range coupling together with their ORD and CD spectra.

The compounds which were chosen for measurement are as follows: Pummerer's keton (I).[5] galanthaminone (II).[6] chamaecynone (III).[2] dihydrochamaecynone (IV).[2] isochamaecynone (V).[2] dihydroisochamaecynone (VI).[2] helvolic acid (VII).[7] two derivatives obtained by base treatment isomerization of helvolic acid: a lacton (VIII) and an ester (IX),[7] murrololone (X),[8] isosinomenine (XI)[9] and occidentalol (XII).[10] Numbering of the A-ring of those is shown in Fig. 1.

There are two possible conformations about the A-ring. The first is that where the carbonyl group is down on the α-side of the molecule (IA type Fig. 2) and in the second

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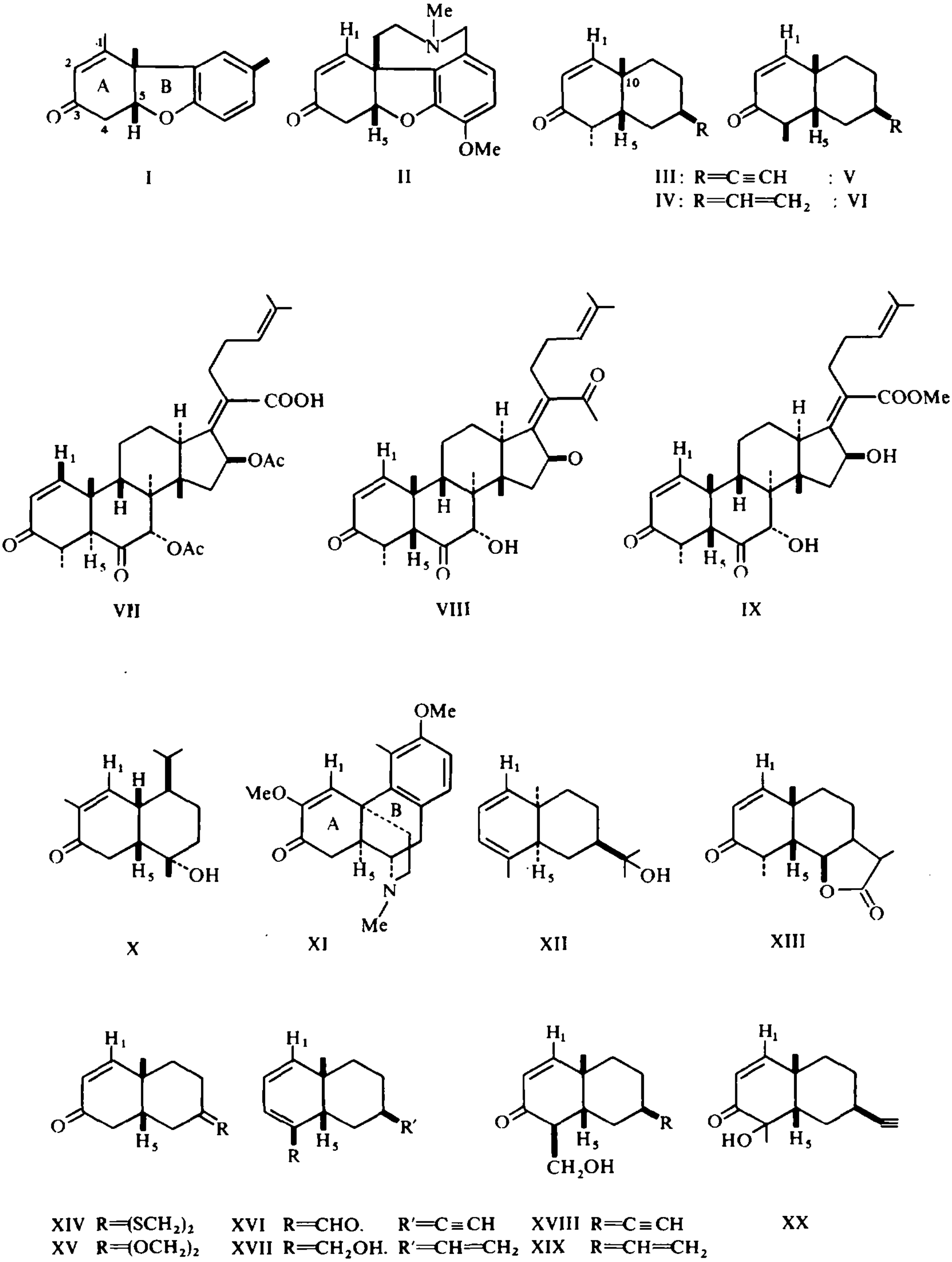


I II

III: R=C≡CH : V

IV: R=CH=CH$_2$: VI

VII VIII IX

X XI XII XIII

XIV R=(SCH$_2$)$_2$

XV R=(OCH$_2$)$_2$

XVI R=CHO. R′=C≡CH

XVII R=CH$_2$OH. R′=CH=CH$_2$

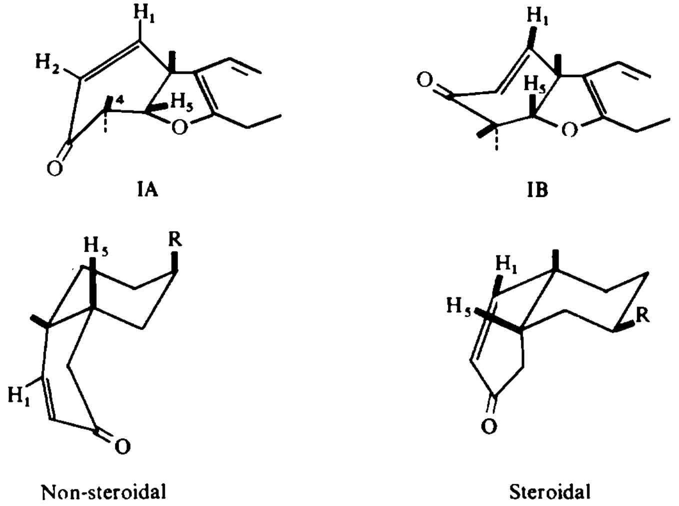
XVIII R=C≡CH

XIX R=CH=CH$_2$

XX

FIG. 1

the carbonyl group is on the β-side (IB type Fig. 2). All hydrogens of the A-ring are not equal and show different chemical shifts. The chemical shift values and coupling patterns of each hydrogen of the A-ring are as follows: ppm (Hz) in $CDCl_3$: 6·43 (d,d, J = 10·2, 2·0), 5·87 (d,d, J = 10·2, 0·7), 4·64 (d,d,d, J = 3·7, 3·0, 2·0), 2·97 (d,d,d, J = 17·4, 3·0, 0·7), and 2·75 (d,d, J = 17·4, 3·7). The peaks can be assigned as H_1, H_2 and H_5 from lower field side by consideration of their chemical shifts. When H_1 is irradiated, H_5 changes to doublet of doublets (J = 3·7, 3·0), and thus the coupling constant between H_1 and H_5 is 2·0 Hz. Although if I adopts a IB type conformation, the H_1-C_1-C_{10}-C_5-H_5 portion of the molecule distorts from a plane, if I adopts a IA type conformation, the same portion exists in a coplaner zig-zag configuration (consider Dreiding models) corresponding to IA and IB. Therefore, the long-range coupling between H_1 and H_5 indicates that I exists in a IA type conformation. This is confirmed by measurement of the vicinal coupling of $H_{4\alpha}$, $H_{4\beta}$ and H_5. If I exists in a IB type conformation, the dihedral angle between $H_{4\alpha}$ and H_5, and of $H_{4\beta}$ and H_5 are *ca.* 160° and 30°, respectively. If I exists in a IA type conformation, the dihedral angles are *ca.* 70° and 45°, respectively. (Dreiding models). The coupling constant between $H_{4\alpha}$ and H_5 is found to be 3·0 Hz and that of between $H_{4\beta}$ and H_5, 3·7 Hz. This is also confirmed by the long-range coupling between H_2 and $H_{4\beta}$ (J=0·7); because $H_{4\beta}$ adopts a quasi-equatorial position in IA type conformation, but not in IB type. This type (H_α—C—CO—C—$H_{\alpha'}$) of long-range coupling is observed when α and α′ hydrogens are placed in a zig-zag coplaner relation.[1, 11,*] All couplings of I have been confirmed by decoupling techniques applied to the corresponding hydrogens.



IA

IB

Non-steroidal

Steroidal

FIG. 2

In a similar manner, the NMR spectrum of galanthaminone (II) was measured and long-range coupling between H_1 and H_5 was observed. By analogy with I, the A-ring of II exists as the A-type conformer in which the carbonyl group is on the α-side.

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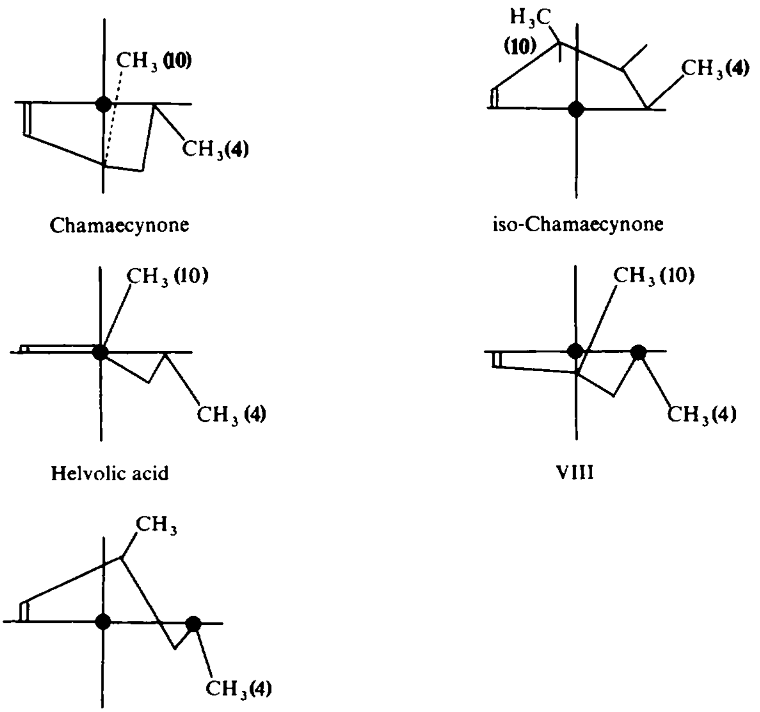
[*] K. Tori reported that an analogous compound of ours, Δ′-5-androsten-3,17-dion shows coupling between H_2 and $H_{4\beta}$ (J = 1·0). Cf. lit. 1c, p. 410.

As briefly reported before.[21] chamaecynone (III) shows a long-range coupling between H_1 and H_5 of 2·2 Hz. Here. we would like to represent additional evidences about the conformation of III. The coupling constant between H_4 and H_5 (3·0 ppm) of III is found to be 4·0 Hz and no appreciable coupling is observed between H_4 and H_2 as expected from its non-steroidal conformation. These facts were also supported by the difference in the chemical shift of the C_4 Me group of III and those of its related compounds in benzene and CCl_4 solutions.[21] By the same procedure. the long-range coupling between H_1 and H_5 of IV was found (Table II). but any appreciable coupling was not observed for V and VI. Therefore. III and IV exist in favorably *cis* non-steroidal conformation. and V and VI are in steroidal conformation in solutions.

The relationship mentioned above is supported not only by the long-range coupling but also by ORD and CD spectra. The conjugated non-planer ketones have been considered as an inherently dissymmetric chromohore. and the helicity rule was advanced for correlating the chirality of the chromohore with the sign of the K-band Cotton effect.[12] while a reverse octant rule was found to be applied for R-band Cotton effect.[13-14] ORD curves of III and IV show a positive Cotton effect in their n-π^* transition region: (c=0·101 dioxane. $[\alpha]_{330}$ −1800°. $[\alpha]_{355}$ +620° (peak). $[\alpha]_{362}$ +400° (trough). $[\alpha]_{370}$ +580° (peak). $[\alpha]_{388}$ 0. $[\alpha]_{700}$ −80°). and (c = 0·092 dioxane. $[\alpha]_{300}$ −2000°. $[\alpha]_{355}$ +560° (peak). $[\alpha]_{361}$ +400° (trough). $[\alpha]_{370}$ +520° (peak). $[\alpha]_{700}$ −20°). Also. $\pi-\pi^*$ transition CD curve of III shows a negative Cotton effect (θ MeOH m. *ca.* 10.000). On the other hand. VI shows a negative Cotton effect



Chamaecynone

iso-Chamaecynone

Helvolic acid

VIII

Fig. 3

(c = 0·098 dioxane. $[\alpha]_{300}$ +1440°. $[\alpha]_{348}$ −680° (trough). $[\alpha]_{356}$ −380° (peak). $[\alpha]_{362}$ −480° (trough). $[\alpha]_{700}$ −20°). Dreiding models of III. IV and VI. deduced from the above results and by consideration of Snatzke's reverse octant rule[14] are consistent with the conclusion from the results of long-range coupling. The octant figures of those compounds are shown in Fig. 3. and they indicate that in the cases of III and IV the carbonyl group is on to α-side and that of VI is placed up on the β-side.

The A/B ring junction of helvolic acid (VII) is trans,[7] and hence we cannot expect to find the above type long-range coupling between H_1 and H_5 of VII; any appreciable coupling was not observed (Table I). On the other hand. its isomers (VIII and IX) show such long-range coupling between H_1 and H_5 of 1·1 Hz. The conformation of the B-ring of VII is said to be in boat form and the B/C ring juncture is *trans*(8β. 9α).[9] However. the C_4 hydrogens of these three compounds always adopt axial positions because there is no appreciable coupling between H_2 and H_4. R-band Cotton effect of CD curves of VIII and its analogues derivatives have been reported to show a positive sign.[7] while the ORD curve of VII shows a negative Cotton effect in that region.[15] The octant values of VIII and its analogous compounds are in accord with the reverse octant rule. However. the carbonyl group of VII adopts a rather flat conformation or slightly on the β-side by examination of its Dreiding model. and hence VII shows a negative Cotton sign. In conclusion. VIII and IX exist in the *cis* configuration and a non-steroidal conformation with the chair form B-ring while VII has *trans* A/B ring junction and a boat form B-ring. The driving force of transformation from VII to VIII is the inversion of the configuration at C_5 (α to β) by which the unstable boat form B-ring is changed to a stable chair form.

NMR data of murrololone (X) are shown in Table I. The spectra of X are measured in $CDCl_3$ and C_6D_6 solution. The chemical shifts and coupling constants of X were confirmed by double resonance techniques and solvent effects. The ring juncture of X has already been established as *cis*.[10] however the coupling between H_1 and H_5 could not be observed. Therefore. the configuration and conformation of X is *cis* and a steroidal conformation exists. This conclusion is supported from a stereochemical point of view. If X adopts a steroidal conformation and if we assume the B-ring of X exists in a chair form. the bulky isopropyl group should take an equatorial position. If this is true. the dihedral angles are as follows: H_1 and H_{10}. 20°; $H_{4\alpha}$ and H_5. 180°; $H_{4\beta}$ and H_5. 60°; H_5 and H_{10}. 60°; approximately by a Dreiding model of X. On the other hand. if X exists in a non-steroidal conformation. the dihedral angles are approximately 60°. 60°. 60°, 30° and 60°. respectively. Therefore. the former model can explain corresponding coupling constants of each dihedral angle while the non-steroidal model can not.

When NMR spectrum of isosinomenine (XI) was measured. any appreciable long-range coupling between H_1 and H_5 could not be observed by the procedure as above. Thus. H_5 takes an axial position for the A-ring and equatorial position for the B-ring. This conclusion is consistent with the well established stereo-chemistry of XI.[16]

As an example of a cyclohexadiene system. a unique sesquiterpene occidentalol (XII) was chosen.[17] The NMR spectrum of XII is very complicated. the assignment of signals is followed by the values of their chemical shifts and coupling constants. The signal of H_1 appears as a broad doublet. Irradiation at 1·72 ppm changes the pattern of H_1 to a double doublet of doublet ($J = 9·0$. 1·1 and 0·9 Hz). The signal of H_1 becomes a double doublet ($J = 9·0$ and 0·9 Hz) when irradiated at 1·72 and 1·52 ppm by triple

TABLE I

	δ_1	δ_2	$\delta_{4\alpha}$	$\delta_{4\beta}$	$\delta_{5\beta}$	δ_{10Me}	$J_{1,2}$	$J_{1,5\beta}$	$J_{2,4\alpha}$	$J_{2,4\beta}$	$J_{4\alpha,5\beta}$	$J_{4\beta,5\beta}$
I	6·43	5·87	2·97	2·75	4·64	1·54	10·2	2·0	0·7		3·0	3·7
III	6·42	5·87		3·00	2·19	1·30	10·2	2·2	0·5		4·0	
VII	7·29	5·86		2·78	2·20[a]	1·44	10·0					
VIII	6·57	5·83		2·91	2·85	1·49	10·5	1·1		0·1		
IX	6·54	5·81		2·83	2·85	1·49	10·5	1·1		0·1		
X	6·94		2·4	2·4	2·2	2·68[b]		0·2			12	6

	δ_1	δ_2	δ_3	δC_{4Me}	δ_5	$J_{1,2}$	$J_{1,3}$	$J_{1,5}$	$J_{2,3}$	$J_{1,4Me}$	$J_{2,4Me}$	$J_{3,4Me}$
XII	5·27	5·86	5·56	1·7	1·3[c] 1·7	9·0	0·9	1·1	5·0	5·0	0·2 0·5	1·5

The data listed in the Table were measured in $DCDl_3$ (5–10%). and TMS as internal standard. δ and *J* values show by ppm and Hz.

[a] 5α-hydrogen.

[b] 10β-hydrogen.

[c] Appeared as complicated multiplets between 1·3–1·7 ppm.

resonance techniques. Although the half part of the signals of H_7 and the signals of the other hydrogens on the B-ring appear as very complex multiplets overlapping each other and cannot be distinguished each other very clearly, irradiation at 5·27 ppm causes a fairly remarkable change on the complex multiplets appearing between 1·35–1·65 ppm. The changes of the other signals by decoupling experiments support the above assignment. These facts indicate that long-range coupling exists between H_1 and H_5. and this type of long-range coupling can be explained by a zig-zag coplaner conformation of the H_1—C_1—C_{10}—C_5—H_5 portion of the molecule. This result definitely excludes the possibility of a *trans* junction of XII. By examination of the Dreiding model of XII and on the assumption that the B-ring exists in a chair form because the bulky isopropyl alcohol group takes an equatorial position. 5_α 10_α-*cis* ring juncture and non-steroidal conformation model for XII are the only one fit to the facts mentioned above. This is one of the stereo-isomers which were pointed out by Mislow and Moscowitz.[18] Unfortunately the signals of H_7 cannot be distinguished from the signals of other hydrogens on the B ring, but the conclusion of the absolute configuration at C_7 of XII by Mislow and Moscowitz[18] seems quite reasonable by consideration of biogenetical relationship of XII and (+)occidol for which the absolute configuration at C_7 was established.[19] If the isopropyl alcohol group takes an axial position, the conformation of the B-ring (and/or A-ring) must be changed. However, this seems very unlikely by the examination of those models judging from our NMR results together with Mislow and Moscowitz. Therefore, the absolute configuration and conformation of (+)occidentalol are confirmed. The misleading result of Ziffer *et al.*[20] may show the sensitivity of the optical method which depends on a little change of conformation and minor conformers play an important role in such cases.[21]

In addition to the examples above, a few examples of the application of this type

TABLE II

	H_1	H_5 (ppm)	$J_{1,5}$ (Hz)
I	6·43	4·64	2·0
II	6·97	4·74	2·2
III	6·42	2·19	2·2
IV	6·38	2·45	2·2
VIII	6·57	2·85	1·1
IX	6·54	2·85	1·1
XII[a]	5·27	1·3 ~ 1·7	1·1
XIII[22]	6·63	1·88	2·0
XIV[23]	6·54		2·0
XV[23]	6·59		1·6
XVI[3]	5·87	2·90	1·5
XVII[3]	5·43	2·01	1·1
V	6·47		
VI	6·47		
VII	7·29	2·20	no appreciable coupling observed
X	6·94		
XI	6·75		
XVIII[24]	5·30		
XIX[25]	5·37		
XX[2]	6·55		

[a] Reported appeared at 5·21 (H_1) and 1·51 (H_5) ppm ($J = 1·0$ Hz). *cf* lit.[17]

long-range coupling to conformational analysis have appeared in the literature[22–24] very recently (Table II). All the cases, except XVIII, XIX[25] and XX,[2] show the same type long-range coupling between H_1 and H_5 indicating they exist in non-steroidal conformation with *cis* A/B ring juncture. However. XVIII. XIX and XX do not show any appreciable coupling between H_1 and H_5. Hence. their conformation is *cis* and of steroidal form. In the case of XVIII and XIX. an α-equatorial hydroxymethyl group forces the molecule to adopt a steroidal form. because if the hydroxymethyl group is in β-axial position (non-steroidal form), a fairly big 1,3-interaction occurred with the C_{10} Me group. The molecular structure of XVIII was also determined by X-ray analysis[26] agreeing with the conclusion based on NMR evidence. Therefore. the configuration and conformation of XVIII are shown to exist in the same configuration in both solid and solution.

Application of this type of long-range coupling to conformational analyses is very useful. especially when the method is applied to α.β-unsaturated cyclohexenone derivatives. Also. when such a type of long-range coupling is observed. one can say $H_1—C_1—C_2—C_3—H_3$ portion of a molecule in a cyclohexane or cyclohexene system is planer. However. when this principle is applied to systems other than cyclohexane or cyclohexene. care is necessary since large couplings have been observed between H_1 and H_5 of α-pinene systems[27, 28] which are not in accord with the coplanarity of W-rule.

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