CONFORMATION OF THE A RING IN 1-OXO AND 3-OXOTRITERPENOIDS. VICINAL INTERPROTON COUPLING CONSTANTS*

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The coupling constants of the protons on the A ring were determined by full analysis of the spin systems in the ^{1}H NMR spectra of 4,4-dimethyl-5α-cholestan-3-one (*XIX*) and 1-oxo and 3-oxo triterpenoids *I*, *XIV*–*XVI*, *XX* and their 2-methyl derivatives *V*, *VI*, *XVII*, *XVIII*, *XXIII* and *XXIV*. From the values of vicinal coupling constants it was inferred that in 2α-methyl-1-oxo and 3-oxo derivatives *V*, *XVII* and *XXIII* the A ring assumes a chair conformation, while in 2β-methyl derivatives *VI*, *XVIII* and *XXIV* a boat conformation. The chair form greatly predominates in 4,4-dimethyl-5α-cholestan-3-one (*XIX*) and in 1-oxotriterpenoid *XX*, while in triterpenoid 3-oxo derivatives *I*, *XIV*–*XVI* a significant amount of boat conformation is present at equilibrium (up to 40%). The solvent shifts and the lanthanide induced shifts of the protons on $C_{(2)}$ lead to the same conclusion.

In many 4,4-dimethyl-5α-steroid and triterpenoid** derivatives with a substituent in the position 2β the A ring exists predominantly or at least partly in boat conformation. The equlibrium of the boat and the chair conformation depends on the nature of the 2β-substituent, on configuration, and the position and the nature of further substituents on $C_{(1)}$ or $C_{(3)}$ and on the presence of the axial methyl groups (4β, 8β, 10β; see[1–4] and the references therein). The number of axial methyl groups on the β-side of the steroid or triterpenoid skeleton seems to have a decisive effect on the equilibrium. In our papers[1,2,5] we have shown that the 8β-methyl group too, although it is remote from the A ring, affects the equilibrium position considerably and causes its shift toward the boat form. This "8β-methyl effect" appears when triterpenoid derivatives are compared with analogous derivatives of 4,4-dimethylsteroids. In the case of 3-oxo derivatives the three 1,3-synaxial interactions between the 4β and 10β-methyl groups and the 2β-substituent (F, Cl, Br, OR, CH_3) destabilize the

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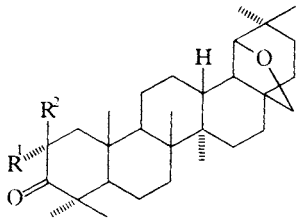
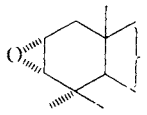
** In this paper we call "triterpenoids" such triterpenoid compounds which contain in addition to the 4α, 4β and 10β-methyl group also the 8β-methyl group. Compounds are called "4,4-dimethylsteroids" which do not contain an 8β-methyl group. In both instances they are compounds of 5α-configuration.

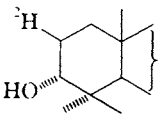
chair form to such an extent as keep the A ring existing practically in the boat form only (see[3,6] and the references therein). The same situation was also observed[2,7] in 2β-bromo-1-oxo derivatives. The elimination of the axial 4β-methyl group leads to an increase in the content of the chair conformation; in 2β-bromo-3-oxo-24-nor-triterpenoids both conformations are populated in an approximately 1 : 1 ratio and in 2β-bromo-5α-cholestan-3-one, which carries only one methyl group (10β) on the A and B rings, the chair form greatly predominates[4,8].



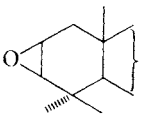
I, $R^1 = R^2 = H$
II, $R^1 = {}^2H$, $R^2 = H$
III, $R^1 = H$, $R^2 = {}^2H$
IV, $R^1 = R^2 = {}^2H$
V, $R^1 = CH_3$, $R^2 = H$
VI, $R^1 = H$, $R^2 = CH_3$
VII, $R^1 = Br$, $R^2 = H$
VIII, $R^1 = H$, $R^2 = Br$



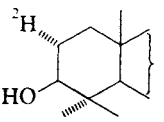
IX



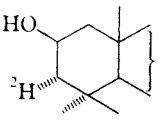
X



XI



XII

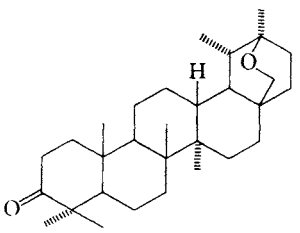


XIII

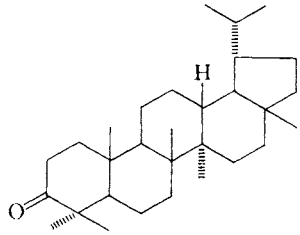
The conformation of the A ring in 3-oxotriterpenoids and 4,4-dimethyl-3-oxosteroids without a substituent in the position 2 was investigated recently by a number of authors (see refs[9–13] and the references therein). In 4,4-dimethyl-3-oxosteroids a deformed chair form[9] was found in crystalline state. In solution the chair form also greatly predominates, the presence of the boat form was not detected[10,11]. Hence, it seems that the only synaxial interaction (between 4β- and 10β-methyl groups) does not increase the energy of the chair form to such an extent as to make it comparable with the energy of the boat form. On the other hand, the conformation of the A ring in 3-oxotriterpenoids and similar compounds with the 8β-methyl group is not yet clear. In crystalline state a distorted boat form was determined in several compounds (20,24-epoxy-11α-hydroxy-24-methyldammaran-3-one[14], 14-serratene-3,21-dione[12], 8αH,14βH-onocerane-3,21-dione[13]), while in 3,21-dioxo-11,13(18)-oleanadien-28-oic acid a deformed chair conformation was observed[15].

As regards the A ring conformation of 3-oxotriterpenoids in solution, the original interpretation[16] of the dipole moment of 3-oxolupane-28-nitrile (*XVI*) was based on the equilibrium of the chair and the boat form. Later it was changed to deformed chair form[17] and on the basis of this conformation the dipole moment of allobetulone[18] (*I*) and the circular dichroism of 3-oxotriterpenoids[19] were also interpreted.

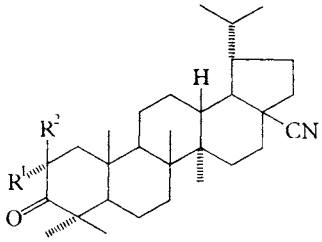
According to molecular mechanics calculations and combined molecular mechanics–quantum chemical calculations, carried out for 4,4-dimethyl-3-oxosteroids and similar bicyclic and tricyclic ketones, the energy of the chair and the boat form differ only very little. It was estimated that the chair form is only about 1–7 kJ . mol^{-1} more stable[9,11,20]. Since the presence of the 8β-methyl group in triterpenoids destabilizes the chair form of the A ring with respect to the boat form by about 2–4 kJ . mol^{-1} (see[1,2,5]), it is probable that in 3-oxotriterpenoids the equilibrium will be shifted closer to the boat form. It may be expected that at equilibrium an observable amount of the boat form will appear. The conformation of the A ring in 1-oxotriterpenoids has not yet been investigated.



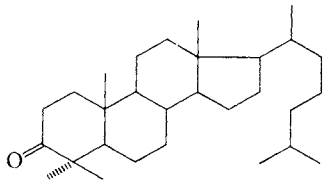
XIV



XV



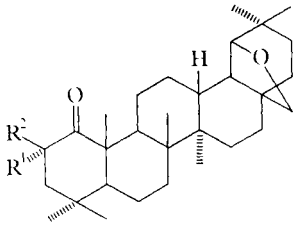
XVI, $R^1 = R^2 = H$
XVII, $R^1 = CH_3$, $R^2 = H$
XVIII, $R^1 = H$, $R^2 = CH_3$



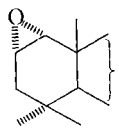
XIX

In this paper we present the results of the study of the A ring conformation in 3-oxotriterpenoids, based on the vicinal coupling constants of the A ring protons. These parameters were obtained by a full analysis of the four-spin systems in

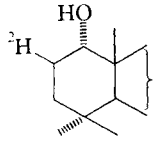
^{1}H NMR spectra of the following triterpenoid 3-ketones: 19β,28-epoxy-18α-oleanan-3-one (*I*, allobetulone, for preparation see[21]), 20β,28-epoxy-18αH,19βH-ursan-3-one (*XIV*, alloheterobetulone[22]), 3-lupanone[23] (*XV*) and 3-oxolupane-28-nitrile[23,24] (*XVI*). For comparison 4,4-dimethyl-5α-cholestan-3-one[25] (*XIX*) was also included in the investigated series. Epimeric 2-methyl-3-oxo derivatives *V*, *VI*, *XVII* and *XVIII* were used as model substances, derived from 19β,28-epoxy-18α-oleanane and 28-lupanenitrile: their preparation and the configuration deduction on $C_{(2)}$ are published in papers[3,24]. Among 1-oxo derivatives we have measured the spectra of 19β,28-epoxy-18α-oleanan-1-one[5] (*XX*) and its 2-methyl derivatives[26] *XXIII* and *XXIV*.



XX, $R^1 = R^2 = H$
XXI, $R^1 = H$, $R^2 = {}^2H$
XXII, $R^1 = R^2 = {}^2H$
XXIII, $R^1 = CH_3$, $R^2 = H$
XXIV, $R^1 = H$, $R^2 = CH_3$
XXV, $R^1 = Br$, $R^2 = H$
XXVI, $R^1 = H$, $R^2 = Br$

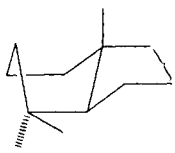


XXVII

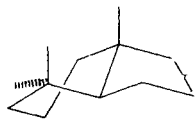


XXVIII

For the identification of the signals of individual hydrogens in the ^{1}H NMR spectra deuterium-substituted ketones *II*–*IV*, *XXI* and *XXII* were prepared. Dideuterio derivatives *IV* and *XXII* were obtained from ketones *I* and *XX* by direct exchange in alkaline medium. The preparation of ketones substituted with deuterium selectively in positions 2α or 2β is based on the known stereochemistry of the opening of epoxides *IX*, *XI* and *XXVII* and analogues[5,21,27,28]. On reduction of 2α,3α-epoxide *IX* with lithium aluminum deuteride 2β-deuterio-3α-ol *X* was formed, and on reduction of 1α,2α-epoxide *XXVII* 2β-deuterio-1α-ol *XXVIII* was obtained. Reduc-



XXIX



XXX

tion of 2β,3β-epoxide *XI* gave 2α-deuterio-3β-ol *XII* as the main product in addition to a small amount of 3α-deuterio-2β-ol *XIII*. Ketones *II*, *III* or *XXI* substituted with deuterium were prepared by oxidation of hydroxy derivatives *X*, *XII* and *XXVIII* with sodium dichromate in acetic acid in the presence of sodium acetate.

EXPERIMENTAL

The ^{1}H NMR spectra were measured on spectrometers Varian HA-100 (100 MHz) in CW-mode and Varian XL-200 (200 MHz) or Bruker WH-360 (360 MHz) in FT-mode. For the measurement solutions of 10—30 mg of triterpenoid in 0·4 ml of deuteriochloroform or hexadeuteriobenzene were used, with tetramethylsilane as internal reference and at room temperature (20—22°C). The typical acquisition parameters in the FT NMR spectra were the following: spectrum width 2 000 Hz, pulse width 4 μs (pulse angle 45°), acquisition time and repetition time 5 s, data points 20 K (zero filling to 32 K), number of accumulations ~100. In order to increase the resolution exponential multiplication and gaussian apodization function were used (with parameters RE = = 0·3 and AF = 0·9). The NMR parameters were extracted from expanded spectra records (1—2 Hz/cm). The difference decoupling spectra were obtained by measuring on-resonance decoupling and off-resonance decoupling spectra of the same sample under identical conditions and their subtracting in the computer memory.

The melting points were determined on a Kofler block and they are uncorrected. 3-Lupanone (*XV*) was prepared according to ref.[23]. M.p. 210—210·5°C (hexane). Ref.[23] gives m.p. 209·5 to 210°C. 4,4-Dimethyl-5α-cholestan-3-one (*XIX*) was prepared according to ref.[25]. M.p. 100 to 102°C (chloroform–methanol), $[\alpha]_D$ +3° (*c* 0·6, chloroform). Ref.[25] gives m.p. 103—104°C, $[\alpha]_D$: 2°.

(2β-^{2}H)-19β,28-Epoxy-18α-oleanan-3α-ol (*X*)

A suspension of 2α,3α-epoxide *IX* (150 mg, see[21]) and lithium aluminum deuteride (140 mg) in ether (100 ml) was refluxed under nitrogen for 7 h. The excess of the reagent was decomposed with ethyl acetate, the mixture was diluted with water, acidified with hydrochloric acid and extracted with ether. The extract was washed with water and dried over sodium sulfate. Ether was distilled off and the residue crystallized from cyclohexane. Yield, 120 mg of 3α-hydroxy derivative *X*, m.p. 287—288°C. For non-deuterated 3α-hydroxy derivative ref.[21] gives m.p. 277—278°C.

(2α-^{2}H)-19β,28-Epoxy-18α-oleanan-3β-ol (*XII*) and
(3α-^{2}H)-19β,28-Epoxy-18α-oleanan-2β-ol (*XIII*)

A suspension of 2β,3β-epoxide *XI* (185 mg, see[21]) and lithium aluminum deuteride (140 mg) in ether (200 ml) and benzene (50 ml) was refluxed under nitrogen for 24 h and worked up as above. The residue was chromatographed on alumina (20 g, activity *II*, Woelm). Elution with benzene gave the starting epoxide *XI* (35 mg). Benzene with 4% of ether eluted 3β-hydroxy derivative *XII* (110 mg), m.p. 271—272°C (chloroform–methanol). For non-deuterated substance ref.[27] gives m.p. 260—261°C. Using the same solvent mixture 2β-hydroxy derivative *XIII* (33 mg) was eluted, m.p. 265—267°C (chloroform–methanol). Ref.[29] gives m.p. 266—268°C for non-deuterated compound.

(2β-^{2}H)-19β,28-Epoxy-18α-oleanan-1α-ol (*XXVIII*)

Reduction of 1α,2α-epoxide *XXVII* (200 mg, see[5,27]) carried out in the same manner as in the

preparation of compound *X* gave 174 mg of 1α-hydroxy derivative *XXVIII*, m.p. 254–256°C (chloroform–methanol). Ref.[27] gives m.p. 254–255°C for the non-deuterated compound.

(2α-^{2}H)-19β,28-Epoxy-18α-oleanan-3-one (*II*)

A mixture of 3β-hydroxy derivative *XII* (63 mg), sodium dichromate dihydrate (120 mg), anhydrous sodium acetate (100 mg) and acetic acid (35 ml) was stirred for 2 h, diluted with water and extracted with ether. The extract was washed five times with water, twice with saturated sodium hydrogen carbonate and water, and dried over sodium sulfate. Ether was distilled off and the residue crystallized from benzene–light petroleum. Yield, 51 mg of ketone *II*, m.p. 235–237°C. For the non-deuterated ketone *I* ref.[21] gives m.p. 235–236°C.

In the same manner (2β-^{2}H)-19β,28-epoxy-18α-oleanan-3-one (*III*), m.p. 235–237°C (benzene–light petroleum) was prepared from 3α-hydroxy derivative *X*. From 1α-hydroxy derivative *XXVIII* (2β-^{2}H)-19β,28-epoxy-18α-oleanan-1-one (*XXI*) was obtained, m.p. 281–282°C (benzene–light petroleum). For ketone *XX* ref.[5] gives m.p. 278–279°C.

(2,2-$^2H_2$)-19β,28-Epoxy-18α-oleanan-3-one (*IV*)

Ketone *I* (150 mg) was added to a solution of sodium (150 mg) in a mixture of dioxane (50 ml) and ^2H_2O (3 ml) and the mixture was refluxed for 7 h. The solvents were evaporated under reduced pressure and dioxane (30 ml) and ^2H_2O (4 ml) were added to the residue. After refluxing for another 6 h the solvents were distilled off under reduced pressure and the residue was extracted with ether and the extract washed 5 times with water. Ether was distilled off and the residue crystallized from benzene–light petroleum to yield 80 mg of ketone *IV*, m.p. 234–236°C.

In the same manner (2,2-$^2H_2$)-19β,28-epoxy-18α-oleanan-1-one (*XXII*), m.p. 280–281°C from benzene–light petroleum was obtained from ketone *XX*.

RESULTS

Unsubstituted Ketones

In the ^{1}H NMR spectra of 3-oxo-derivatives *I*, *XIV*–*XVI* and *XIX*, measured in deuteriochloroform and in some instances in hexadeuteriobenzene, the signals of hydrogens on $C_{(2)}$ are shifted downfield from the methylene envelope and they form a multiplet in which all 16 lines or at least the majority of them could be identified. The multiplet of one of the hydrogens on $C_{(1)}$ (1βH, see below) appears on the left end of the methylene and methine signals and in some instances it is partly overlapped by other signals. Using decoupling experiments and differential decoupling the majority or all of the 8 lines of 1βH could be found in the mentioned ketones. Ketone *XVI* was an exception when measured in deuteriochloroform where the signal 1βH is overlapped by other signals (probably signals of protons in the vicinity of the nitrile group), so that only its position could be ascertained by the decoupling experiment. The signal 1αH is shifted upfield in all 3-oxo derivatives and it is overlapped by other signals. Using decoupling and differential decoupling (irradiation of the $C_{(2)}H_2$ multiplet) it was found that it appears in the region of δ 1·40 (in deuterio-

chloroform). The same value was found in 2α-deuterio derivative *II* by means of spin-tickling and in 2,2-dideuterio derivative *IV* it was calculated from the ratio of the intensities of the lines in the doublet of 1βH. Similarly the signal of 1αH in ketones *I*, *XVI* and *XIX* was found by decoupling experiments when measured in hexadeuteriobenzene (about δ 1·1).

The assignment of the signals 2αH and 2βH in ketone *I* was carried out on the basis of the spectra of deuterated ketones *II*, *III* and *IV*. The assignment of the signals of hydrogens on $C_{(1)}$ is based on the long-range coupling between 1αH and 10β-methyl group and it follows from decoupling experiments; irradiation of the multiplet of 1αH in ketones *I* and *XIV* (about δ 1·42 in deuteriochloroform) caused the doublet of the 10β-methyl at $\delta \sim 0{\cdot}95$ ($J \sim 0{\cdot}7$ Hz) to collapse, while on irradiation of the multiplet 1βH ($\delta \sim 1{\cdot}94$) the doublet did not change. In ketone *XV* the irradiation of the doublet of the 10β-methyl group (δ 0·94, $J \sim 0{\cdot}9$ Hz) led to a sharpening of the lines of 1αH in the δ 1·40 region, while the lines in the multiplet of 1βH remained unchanged. In other 3-ketones the signals were assigned on the basis of the analogy and the similarity of the vicinal coupling constant values.

In the spectra of 1-oxo derivative *XX* decoupling and differential decoupling experiments identified the majority of the lines in the multiplets of all four hydrogens on the A ring. The assignment of the signals to individual hydrogens in the position 2 and 3 was carried out on the basis of the spectra of deuterated ketones *XXI* and *XXII* and the vicinal coupling constant values observed.

The four-spin systems in 3-oxo and 1-oxo derivatives *I*, *XIV–XVI*, *XIX* and *XX* were analysed as ABCD spectra by a simulation-iterative program*. Starting values of the parameters J and ν for the iterative procedure were obtained by analysis in ABPX approximation (see[30]) or first order analysis or estimated on the basis of spectra simulation. All vicinal constants were taken as positive while the geminal constants as negative. In all instances the iterative calculation was carried out for at least two sets of experimental data (line frequencies) and for several sets of the starting values of J and ν. The optimalized values of the J and ν parameters, obtained by simulation-iterative calculation from various sets, were in good agreement within the $\pm 0{\cdot}1$ Hz limits. The spectra simulated on the basis of these parameters were in good agreement with the experimental spectra; the maximal differences between the line frequencies found and calculated were less than 0·1 Hz. The resulting values of the coupling constants (rounded up to 0·1 Hz) and chemical shifts (rounded up to 0·01 ppm) are listed in Tables I and II. The found and the simulated spectrum of ketone *I* are compared in Fig. 1. In a similar manner the spectra of deuterated ketones *II*, *III* and *XXI* were analysed as ABC systems.

If the lines of some protons could not be identified in the spectrum, the correspon-

* The program was written by Dr J. Pecka of the Department of Organic Chemistry, Charles University, Prague.

TABLE I

Coupling constants (in Hz) and chemical shifts (δ-scale, ppm) of protons on the A ring in 3-oxo derivatives

Ketone[a]	Substituents on $C_{(2)}$	Solvent[b]	ν^c (MHz)	$J_{1\alpha,2\alpha}$	$J_{1\alpha,2\beta}$	$J_{1\beta,2\alpha}$	$J_{1\beta,2\beta}$	$-J_{1\alpha,1\beta}$	$-J_{2\alpha,2\beta}$	$\delta_{1\alpha H}$	$\delta_{1\beta H}$	$\delta_{2\alpha H}$	$\delta_{2\beta H}$
I	—	Ch	100	~7·9	9·4	4·4	7·8	13·2	15·7	(1·42)	1·94	2·43	2·49
			200	7·9	9·5	4·5	7·8	13·3	15·7	(1·45)	1·92	2·43	2·50
			360	7·8	9·5	4·4	7·8	13·2	15·7	(1·42)	1·94	2·43	2·50
		Bz	100	7·6	9·8	4·2	7·8	13·1	15·7	(1·08)	1·60	2·26	2·32
II	α-^{2}H	Ch	100	—	~9·5	—	7·7	13·2	—	(1·42)	1·94	—	2·48
III	β-^{2}H	Ch	100	~7·7	—	4·4	—	13·2	—	(1·42)	1·93	2·41	—
IV	$^2H_2$	Ch	100	—	—	—	—	13·2	—	(1·42)	1·92	—	—
XIV	—	Ch	100	~7·9	9·4	4·4	7·7	13·2	15·7	(1·42)	1·95	2·42	2·50
XV	—	Ch	200	7·6	9·9	4·4	7·6	13·3	15·7	(1·40)	1·92	2·41	2·49
XVI	—	Ch	200	7·5	10·0	4·3	7·6	(13·3)[d]	15·7	(1·40)	(1·93)	2·41	2·51
		Bz	200	7·4	10·3	4·2	7·6	13·0	15·6	(1·05)	1·56	2·24	2·32
XIX[e]	—	Ch	200	5·6	12·9	3·4	6·6	13·2	15·3	(1·38)	1·95	2·32	2·62
		Bz	200	5·6	12·9	3·4	6·5	13·2	15·2	(1·10)	1·61	2·23	2·39
V[f]	α-CH_3	Ch	200	—	13·2	—	5·7	13·0	—	~1·00	2·06	—	2·78
		Bz[g]	100	—	~13	—	≦5·8	13·2	—	[h]	1·82	—	2·55
XVII[f]	α-CH_3	Ch	200	—	13·1	—	5·7	13·0	—	0·93	2·04	—	2·78
		Bz	200	—	13·2	—	5·7	~13·0	—	~0·78	1·77	—	2·53
VI[f]	β-CH_3	Ch	200	11·3	—	9·0	—	13·2	—	1·97	1·23	2·83	—
		Bz[g]	100	~11	—	~9	—	[h]	—	[h]	[h]	2·49	—
XVIII[f]	β-CH_3	Ch	200	11·1	—	9·2	—	13·2	—	~1·95	1·22	2·83	—
		Bz	200	11·2	—	9·2	—	13·2	—	1·63	[h]	2·49	—

[a] The values given in brackets were not refined during the iterative process; the accuracy of the coupling constants is 0·1 to 0·2 Hz, a lower accuracy is indicated by ~; [b] Ch deuteriochloroform, Bz hexadeuteriobenzene; [c] the working frequency of the spectrometer used; [d] the value is taken from the spectra of ketones *I*, *XIV* and *XV*; [e] ref.[10] gives for ketone *XIX* in CCl_4 the following vicinal coupling constants: 5·1, 13·7, 3·1 and 6·4 Hz; in C_6H_6: 5·1, 14·1, 3·1 and 6·6 Hz; [f] J_{2H,CH_3} = 6·4–6·5 Hz; [g] the values taken from ref.[3]; [h] the value is not determined.

TABLE II

Coupling constants (in Hz) and chemical shifts (δ-scale, ppm) of protons on the A ring in 1-oxo derivatives

Ketone[a]	Substituents on $C_{(2)}$	Solvent[b]	ν[c] (MHz)	$J_{2\alpha,3\alpha}$	$J_{2\beta,3\alpha}$	$J_{2\alpha,3\beta}$	$J_{2\beta,3\beta}$	$-J_{3\alpha,3\beta}$	$-J_{2\alpha,2\beta}$	$\delta_{3\alpha H}$	$\delta_{3\beta H}$	$\delta_{2\alpha H}$	$\delta_{2\beta H}$
XX	—	Ch	200	4·9	12·4	5·0	5·6	13·6	13·3	1·63	1·79	2·09	2·93
		Bz	200	4·7	12·8	4·8	5·7	(13·6)[d]	13·2	1·41	1·45	2·01	2·67
XXI	β-^{2}H	Ch	100	~5·0	—	5·2	—	13·7	—	~1·62	1·78	~2·10	—
XXII	$^2H_2$	Ch	100	—	—	—	—	13·7	—	1·62	1·78	—	—
XXIII[c]	α-CH_3	Ch	200	—	13·4	—	5·6	13·3	—	1·26	1·76	—	3·20
XXIV[f]	β-CH_3	Ch	200	<6·7	—	>12·1	—	—	—	~1·5	~1·5	2·61	—

[a–c] See the notes to Table I; [d] the value is taken from the spectrum in C^2HCl_3; [e] $J_{2H,CH_3} = 6{\cdot}2$ Hz; [f] $J_{2H,CH_3} = 6{\cdot}7$ Hz.

ding parameters were left constant during the iterative process and they were not refined (in the Tables I and II these parameters are given in brackets). The chemical shift of 1αH in all 3-oxo derivatives is an example. However, in this case, the iterative procedure was repeated with different $\delta_{1\alpha H}$ values (in the interval up to +0·3 and −0·5 ppm from the $\delta_{1\alpha H}$ values given in Table I). In this way it was found that the value $\delta_{1\alpha H}$ affects the resulting coupling constant values only negligibly (maximally in the ±0·1 Hz range). The spectra of ketones *I*, *XVI*, and *XX* were measured at two frequencies (100 and 200 MHz) and the spectrum of ketone *I* also at 360 MHz. The agreement of the *J* values obtained by the iterative procedure from these spectra was better than 0·1 Hz (for ketone *I* the values are compared in Table I) and it confirms the correctness of the analysis of the four-spin system.

The NMR spectrum of 4,4-dimethyl-5α-cholestan-3-one (*XIX*) was analysed earlier by Burkert and Allinger[10]; however, some coupling constant values (especially $J_{1\alpha,2\beta}$, see Table I, note[e]) differs considerably from the values found by us. These differences may be caused by the fact that in ref.[10] the analysis was carried out only on the basis of the multiplet $C_{(2)}H_2$ and from the 100 MHz spectrum.

2-Methyl Ketones

The multiplet $C_{(2)}H$ in the spectra of all 2-methyl-3-oxo- and 2-methyl-1-oxo deriva-

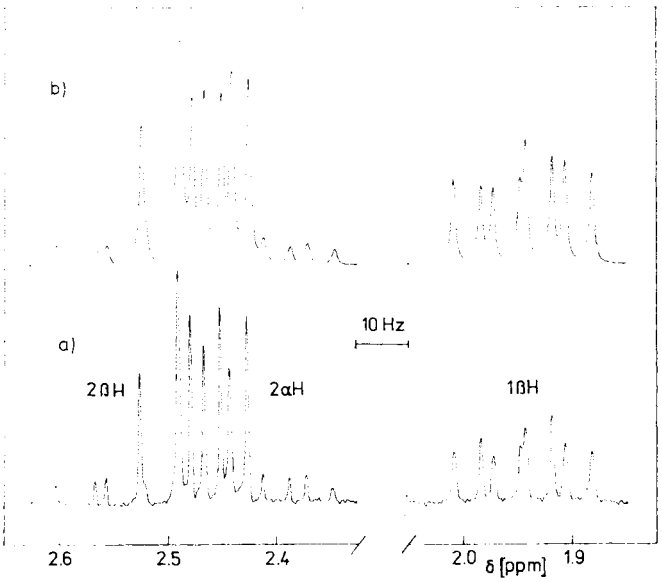


FIG. 1

Part of the ^{1}H NMR spectrum of allobetulone (*I*) in deuteriochloroform at 200 MHz; *a* observed spectrum, *b* calculated spectrum

tives is shifted sufficiently downfield and its identification was not difficult. The signals of the hydrogen atoms on $C_{(1)}$ in 2-methyl-3-oxo derivatives and the hydrogens on $C_{(3)}$ in 2-methyl-1-oxo derivatives were found by means of decoupling experiments. In the same manner the doublet of the methyl group in position 2 was also identified. The assignment of the signals of 1αH and 1βH in 2-methyl-3-oxo derivatives is again based on the long-range coupling of 1αH with 10β-methyl group, and it was confirmed by decoupling experiments. In 2-methyl-1-oxo derivatives the assignment was carried out on the basis of the measured vicinal coupling constant values.

All spectra were analysed as first order spectra. The resulting values are given in Tables I and II. In ketones *V, VI, XVII, XVIII* and *XXIII* the differences of the chemical shifts of the A ring hydrogens are sufficiently high, so that the first order coupling constants represent a very good approximation to the real *J* values. However, in 2β-methyl-1-oxo derivative *XXIV* the difference of the chemical shifts of 3αH and 3βH is evidently very small even in the 200 MHz spectrum. Using a decoupling experiment the region was determined – only approximately – where both signals appear, but we were unable to identify their lines sufficiently well for a complete analysis of the system. The observed values of the first order coupling constants (12·1 and 6·7 Hz, from a 200 MHz spectrum) may differ from the real values by 1–2 Hz; for comparison the first order constants from a 100 MHz spectrum were ~11 and ~8 Hz, respectively.

DISCUSSION

For the detection of the boat conformation of the A ring and for the assessment of its participation at equilibrium from the vicinal coupling constant values, characteristic values ^3J of the basic A ring conformations – boat and chair – must be known. One way of obtaining these values is their calculation from torsion angles φ between individual hydrogen atoms. However, the results are problematic both because they depend on the choice of the $J = f(\varphi)$ relation, and because the true geometry of neither the chair nor the boat form of the A ring is known precisely. Depending on the presence of the 8β-methyl group, the position of the carbonyl group and the difference in the rest of the skeleton, the chair form can be distorted in various ways (for example flattened) and its true geometry in 1-oxo and 3-oxo-triterpenoids and 4,4-dimethyl-3-oxosteroids may differ considerably. In the boat form the situation is still more complex because this conformation is more flexible and can assume various spatial arrangements by pseudorotation between two classical boat forms *XXIX* and *XXX*. Moreover it can be flattened or otherwise deformed in various ways. According to the results of X-ray diffraction[9,12–15] the geometry of both the chair and the boat form in various 3-oxo derivatives differs in crystalline state.

It is further possible to take the characteristic ^3J values for the chair and the boat form from model compounds. We chose this approach for the study of the conformation of the A ring of 1-oxo and 3-oxo-triterpenoids *I*, *XIV–XVI* and *XX*. As model compounds we used corresponding ketones with the methyl group on $C_{(2)}$. According to the analogy with the ketones substituted on $C_{(2)}$ with various polar groups (see refs[2–4,6,7,21,31,32] and the references therein) it may be expected that the conformation of the A ring in 2α-methyl ketones *V*, *XVII* and *XXIII* will correspond to the chair form, while the conformation in 2β-methyl ketones *VI*, *XVIII* and *XXIV* will be that of the boat form. In the case of 2-methyl derivatives of allobetulone *V* and *VI* this assumption was already confirmed in ref.[3].

The use of 2-methyl derivatives as model compounds includes the following assumptions: *a*) the substitution of the hydrogen atom by a methyl group does not change the geometry of the A ring substantially, either in chair or in boat form, *b*) the methyl group does not affect the values of the vicinal coupling constants, *c*) the population of the boat form in 2α-methyl ketones and the chair form in 2β-methyl ketones is negligible, or at least so low that it does not affect the coupling constant values significantly. Since these assumptions need not be fulfilled completely, this approach represents a certain approximation. On the other hand, the model compounds are derived directly from the ketones investigated, so that they include inherently the distortions of the chair and the boat form, given by the triterpenoid skeleton and the position of the carbonyl group.

Conformation of 2-Methyl Ketones

In 2α-methyl-3-oxo derivatives *V* and *XVII* the value of $J_{1\alpha,2\beta}$ (13·2 Hz) corresponds to a diaxial arrangement of the hydrogens and the value $J_{1\beta,2\beta}$ (5·7 Hz) to an equatorial-axial arrangement. These values are in agreement with the chair conformation of the A ring. Practically the same values (13·1 and 6·2 Hz) were obtained in 2α-bromo-3-oxo derivative[3] *VII* and in the analogous chloro derivative[6]. In 2β-methyl-3-oxo derivatives *VI* and *XVIII* $J_{1\alpha,2\alpha}$ (11·2 Hz) and $J_{1\beta,2\alpha}$ (9·1 Hz) are incompatible with the chair form and they correspond to the values found for the boat form in 2β-bromo ketone[3,4] *VIII* (11·2 and 9·4 Hz) and in the corresponding chloro ketone[6] (10·9 and 9·2 Hz). The chair form of the A ring in 2α-bromo and 2α-chloro derivatives and the boat form in 2β-isomers was also demonstrated by other spectral methods[6,21,31]. The mentioned agreement of the coupling constants of 2-methyl, 2-bromo and 2-chloro derivatives shows that the population of the boat form in 2α-methyl derivatives *V* and *XVII* and the population of the chair form in 2β-methyl derivatives *VI* and *XVIII* is very low. The agreement between 2-methyl ketones and the ketones with a polar substituent in position 2 (Br, Cl, OCH_3)[3,4,6] is also manifested in the chemical shifts of the protons on $C_{(1)}$. In all 2α-isomers (chair form) the signal 1αH is shifted upfield in comparison with the signal 1βH,

while in 2β-isomers with the A ring in boat form the opposite is true: the upfield signal belongs to 1βH.

From the coupling constants $J_{1\alpha,2\alpha}$ and $J_{1\beta,2\alpha}$ in 2β-methyl-3-oxo derivatives *VI* and *XVIII* the torsion angles φ between the hydrogens can now be assessed and the geometry of the boat form thus determined more accurately. The use of the Karplus equation in its simplest form, $J = k_i \cos^2 \varphi$, with the coefficients found by Abraham and Holker[32] ($k_1 = 12{\cdot}4$ for $0° < \varphi < 90°$; $k_2 = 14{\cdot}3$ for $90° < \varphi < 180°$) leads to the torsion angles $\varphi_{1\alpha,2\alpha} = 18°$ and $\varphi_{1\beta,2\alpha} = 143°$. Although these values are a mere approximation of the true angles, they correspond approximately to the internal torsion angles Θ (the torsion angles of the $C_{(3)}-C_{(2)}-C_{(1)}-C_{(10)}$ bonds), determined from the X-ray diffraction data of triterpenoid 3-oxo derivatives which when in crystalline state have the A ring in boat conformation: 14-serratene-3,21-dione[12] (Θ = 18°), 8αH,14βH-onocerane-3,21-dione[13] (Θ = = 14°) and 20,24-epoxy-11α-hydroxy-24-methyldammaran-3-one[14] (Θ = 10°). The mentioned values $\varphi_{1\alpha,2\alpha}$ and $\varphi_{1\beta,2\alpha}$ indicate that the geometry of the boat form (in solution) corresponds to the twist form which is closer rather to the classical boat form *XXIX* than the form of *XXX*. We also came to the same conclusion in the case of some 1α,2β-disubstituted triterpenoids[2].

In 2α-methyl-1-oxo derivative *XXIII* the values of $J_{2\beta,3\alpha}$ (13·4 Hz) and $J_{2\beta,3\beta}$ (5·6 Hz) are again in agreement with the literature[2] data for 2α-bromo ketone *XXV* (13·8 and 5·8 Hz) and they agree with the chair form. In the case of 2β-methyl-1-oxo derivative *XXIV* the real coupling constant values could not be determined, but only the limit values $J_{2\alpha,3\alpha} < 6{\cdot}7$ and $J_{2\alpha,3\beta} > 12{\cdot}1$ Hz. However, even these values and mainly their sum $\sum J = 18{\cdot}8$Hz (obtained from the spectrum with a sufficient accuracy) are in contradiction with the chair form and indicate that in this isomer the boat form is highly predominant. The observed values are close to the constants determined in 2β-bromo ketone *XXVI* (5·6 and 13·8 Hz, $\sum J = 19{\cdot}4$ Hz) in which the boat form was already demonstrated[2]. Even in the 1-oxo series an agreement is observed between 2-methyl and 2-bromo derivatives[2] as regards the chemical shifts of protons on $C_{(3)}$: in the chair form of the 2α-isomers *XXIII* and *XXV* the axial 3αH is shifted upfield with respect to the equatorial 3βH, while in the case of the 2β-isomers *XXIV* and *XXVI* in the boat form the chemical shifts of 2αH and 3βH differ only negligibly.

Conformation of 1-Oxo Derivative XX

From a comparison of the coupling constants (Table II) of ketone *XX* and the model compounds *XXIII* and *XXIV* it follows that the preferred conformation of the A ring both in deuteriochloroform and in hexadeuteriobenzene is the chair form. This is also evidenced by the high value of $J_{2\beta,3\alpha}$ and the low value of $J_{2\alpha,3\beta}$. The $J_{2\beta,3\alpha}$ value (12·4–12·8 Hz) is slightly lower than in the model compound XXIII

(13·4 Hz), which might be caused both by the fact that the geometry of the chair form of ketones *XX* and *XXIII* differ slightly, and by the fact that in ketone *XX* only a small amount of the boat form is present at equilibrium. However, the relatively low value of $J_{2\alpha,3\beta}$ (~5 Hz) in comparison with the high value characteristic of the boat form (~13 Hz) excludes any significant population of the boat form.

Conformation of 3-Oxo Derivatives I, XIV–XVI *and* XIX

In principle the coupling constant values (Table I) of 4,4-dimethyl-5α-cholestan-3-one (*XIX*) are in agreement with the chair conformation of the A ring. The negligibly lower value of $J_{1\alpha,2\beta}$ and the higher value of $J_{1\beta,2\beta}$ in comparison with 2-methyl-3-oxotriterpenoids *V* and *XVII* can be caused by the small differences in the geometry of the chair form of the steroid ketone *XIX* and the triterpenoid model substances, or the presence of a small amount of the boat form. Hence, the preferred conformation of the A ring in 4,4-dimethylsteroid 3-oxo derivative *XIX* is the chair form which is in agreement with the conclusions in refs[10,11].

In the case of 3-oxotriterpenoids *I*, *XIV–XVI* the coupling constant values in both solvents used differ completely from the constants found in 4,4-dimethyl-5α-cholestan-3-one (*XIX*), in 1-oxo derivative *XX* and in the model compounds *V*, *VI*, *XVII* and *XVIII*. These constants do not correspond either to the chair or the boat form: the value of $J_{1\alpha,2\beta}$ is excessively low and that of $J_{1\beta,2\beta}$ is too high in comparison with the model substances *V* and *XVII* for the chair form; the values of $J_{1\alpha,2\alpha}$ and $J_{1\beta,2\alpha}$ are much lower than in the model compounds *VI* and *XVIII* for the boat form. The observed values are between the values expected for the chair form and for the boat form. Hence, it is possible that they are time averaged constants corresponding to a rapid interconversion of both forms and that the proportion of both forms at equilibrium is comparable.

Allobetulone (*I*) and alloheterobetulone (*XIV*) display practically identical coupling constant values; the same agreement may also be observed in 3-lupanone (*XV*) and 3-oxolupane-28-nitrile (*XVI*). However, the constants of these two groups of substances differ slightly. The differences are also evident when the constants found in deuteriochloroform and in hexadeuteriobenzene are compared. The mean values of the vicinal coupling constants for the mentioned types of ketones and for both solvents are listed in Table III. Although the differences observed are not large, they exceed the experimental errors (0·1 Hz) and their trend in all coupling constants indicates that the proportion of the boat and the chair form at equilibrium changes in dependence on the type of skeleton and the solvent. The differences in $J_{1\alpha,2\beta}$ values are especially significant, where the highest sensitivity to a change of the equilibrium may be expected. These differences do not appear in cases where the A ring exists practically in one of the conformations only. From Table I it is evident that in 4,4-dimethyl-5α-cholestan-3-one (*XIX*) the values of all coupling constants

are in perfect agreement in both solvents. Nor are significant differences evident in the dependence on the type of skeleton and the solvent in the case of model compounds *V*, *VI*, *XVII* and *XVIII*.

From the values of the coupling constants given in Table III we tried to estimate the population of the boat form in ketones *I*, *XIV*–*XVI*. As values characteristic of the chair and the boat form two of the four *J* values for each form could be taken directly from the model compounds *V*, *VI*, *XVII* and *XVIII*: $J_{1\alpha,2\beta}$ and $J_{1\beta,2\beta}$ for the chair form and $J_{1\alpha,2\alpha}$ and $J_{1\beta,2\alpha}$ for the boat form. Their mean values (equal for both solvents and both types of skeletons) are included in Table III. Further characteristic constants had to be estimated. Under the assumption that the torsion angles between 1αH and 2αH and between 1βH and 2βH are similar, we envisaged for $J_{1\alpha,2\alpha}$ in chair form the same value as for $J_{1\beta,2\beta}$ (5·7 Hz). Analogously in the boat form we used as $J_{1\beta,2\beta}$ the found value for $J_{1\alpha,2\alpha}$ (11·2 Hz). On the basis of the mentioned characteristic values for both conformers the population of the boat form could now be estimated from two coupling constants ($J_{1\alpha,2\alpha}$ and $J_{1\beta,2\beta}$) for all four sets of experimental data. The results (Table III) are mutually in good agreement and they range between 31 and 40%.

TABLE III

Characteristic values of the vicinal coupling constants and the estimated populations of the boat form in 3-oxotriterpenoids

Ketone	Solvent[a]	$J_{1\alpha,2\alpha}$	$J_{1\alpha,2\beta}$	$J_{1\beta,2\alpha}$	$J_{1\beta,2\beta}$	Mean value of the boat population, %
		(boat %)				
I, *XIV*	Ch	7·9	9·5	4·5	7·8	
		(40)	(39)	(39)	(38)	39
I	Bz	7·6	9·8	4·2	7·8	
		(35)	(35)	(36)	(38)	36
XV, *XVI*	Ch	7·6	10·0	4·3	7·6	
		(35)	(33)	(38)	(35)	35
XVI	Bz	7·4	10·3	4·2	7·6	
		(31)	(30)	(35)	(35)	33
chair	Ch, Bz	5·7[b]	13·2[c]	1·4[b]	5·7[c]	
boat	Ch, Bz	11·2[c]	3·6[b]	9·1[c]	11·2[b]	

[a] Ch deuteriochloroform, Bz hexadeuteriobenzene; [b] see text; [c] the values are taken from model compounds *V*, *VI*, *XVII* and *XVIII*.

For the remaining two characteristic J values ($J_{1\beta,2\alpha}$ in the chair form and $J_{1\alpha,2\beta}$ in the boat form) relatively low values may be expected on the basis of the estimation from the molecular models. When considering that the values are probably in the 1 – 3 Hz range, the calculation of the boat form population for four sets of experimental coupling constants leads to results ranging from 20 to 43%, which is in agreement with the results mentioned above. In order to obtain more consistent values for populations we used the following procedure: from the experimental values $J_{1\beta,2\alpha}$ and $J_{1\alpha,2\beta}$, found in ketones *I* and *XIV* in deuteriochloroform, we calculated the above mentioned characteristic J values for both forms so that the resulting values of populations should agree with the values obtained from $J_{1\alpha,2\alpha}$ and $J_{1\beta,2\beta}$ (~39%). This procedure leads in the case of the chair form to $J_{1\beta,2\alpha}$ = = 1·4 Hz and in the case of the boat form to $J_{1\alpha,2\beta}$ = 3·6 Hz. The value 1·4 Hz is close to the value of 1·2 Hz found for the corresponding coupling constant in 4-tert-butylcyclohexanone[33]. We could not find any suitable analogy for the value 3·6 Hz. From these characteristic J values the population of the boat form was then calculated for the remaining sets of the experimental data. The populations obtained in this manner and their mean values are listed in Table III.

In view of the approximate character of the method used the mentioned mean values of the population should be considered as a rough approximation. So it cannot be expected that the precision will be higher than ±10%. However, the values of the population are burdened rather by a systematic error, given by the characteristic J values used, so that small differences in the population, caused by the solvent effect, or the differences in skeletons are probably realistic. To sum up it may be stated that the vicinal coupling constants clearly indicate that in 3-oxotriterpenoids in solutions the boat form is represented significantly and that its content can be up to 40%. The results of further physical measurements also lead to the same conclusion and to similar values for the boat form population[26].

On the basis of the equilibrium of the chair and the boat form of the A ring the benzene-induced shifts of protons on $C_{(2)}$ in 3-oxotriterpenoids *I* and *XVI* (see

TABLE IV

Benzene induced shifts of 2αH and 2βH $\Delta\delta^a$

Proton	*I*	*XVI*	*XIX*	*XX*	*V*	*XVII*	*VI*	*XVIII*
2α	−0·17	−0·17	−0·09	−0·08	—	—	−0·34	−0·34
2β	−0·18	−0·19	−0·23	−0·26	−0·23	−0·25	—	—

[a] $\Delta\delta = \delta$ (in $C_6{}^2H_6$) − δ (in C^2HCl_3).

Table IV) may also be interpreted. In 4,4-dimethyl-5α-cholestan-3-one (*XIX*) and in 1-oxotriterpenoid *XX*, where the chair form strongly predominates, the aromatic solvents cause a higher upfield shift of the axial 2βH than in the case of the equatorial 2αH, which is in agreement with literature[34]. The high solvent shift also appears in axial 2βH in 2α-methyl-3-oxo derivatives *V* and *XVII* and in axial (in boat form) 2αH in 2β-methyl-3-oxo derivatives *VI* and *XVIII*. In the case of allobetulone (*I*) and 3-oxolupane-28-nitrile (*XVI*) both protons on $C_{(2)}$ display almost identical solvent shift values, between the values typical of axial and equatorial protons, which correspond both in the case of 2αH and 2βH to averaged values of the shifts in chair and boat form. Both hydrogens thus do not behave as axial and equatorial hydrogens in α-position to the carbonyl, but they display a certain "average behaviour", corresponding to the fact that their relative position with respect to the carbonyl group is mutually exchanged when the A ring passes from the chair to the boat form.

A similar situation also appears in the case of the shifts induced by the lanthanide shift reagent. An addition of europium(III)-tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octane-dionate) to the solutions of allobetulone (*I*) and 3-lupanone (*XIV*) in deuteriochloroform leads to small changes of the multiplet $C_{(2)}H_2$ pattern only, although the downfield shifts of this multiplet are considerable (when we added the reagent gradually we achieved in both ketones shifts up to ~3 ppm, when a broadening of the lines and spectra degeneration already took place, caused by the fact that the difference of the chemical shifts 2αH and 2βH were close to zero). As found on the basis of spectra simulation the changes observed of the multiplet pattern correspond to negligible changes in the difference of the chemical shifts of 2αH and 2βH only (less than 0·1 ppm). Both protons display approximately the same induced shifts (the ratio of the induced shifts 2αH/2βH was found ~1·03 in both ketones *I* and *XIV*). For the equatorial hydrogen a high value may be expected, while for the axial a low one. For example in the case of 4-tert-butylcyclohexanone the ratio of induced shifts of the equatorial and the axial hydrogen on $C_{(2)}$ was found to be about 1·4 (see ref.[35]).

Finally, it may be stated that the conclusions on the conformation of the A ring of 3-oxo- and 1-oxotriterpenoids and 4,4-dimethyl-3-oxosteroids are in full agreement with the general effects which we have mentioned in refs[1,2,5]: *a*) the higher population of the boat form in 3-oxotriterpenoids *I*, *XIV*–*XVI* in comparison with 4,4-dimethyl-5α-cholestan-3-one (*XIX*) agrees with the observed effect of the 8β-methyl group which causes a shift of the equilibrium to the boat form (8β-methyl effect)[1]; *b*) the higher population of the boat form in 3-oxotriterpenoids in comparison with 1-oxotriterpenoid *XX* agrees with the differences observed[2,5] between the derivatives substituted in position 3 and derivatives substituted in position 1 (the nature of this effect is not yet clear, for a more detailed discussion see ref.[2]).

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