CONFORMATION OF RING A OF 1,2-DISUBSTITUTED TRITERPENES. GEOMETRY AND STABILITY OF THE BOAT FORM*

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*Dedicated to Professor F. Šantavý on the occasion of his 60th birthday.*

Conformation of ring A in derivatives of 19β,28-epoxy-18α-oleanane (*I*) which contain in the positions 1 and 2 bromine, hydroxyl, acetoxyl or carbonyl group, has been derived on the basis of infrared and ultraviolet spectra, circular dichroism and PMR spectra. In derivatives containing 2β-bromine the boat form predominates at equilibrium, while in derivatives with an oxygen function in the 2β-position the chair form prevails. The geometry of the boat form of 1α,2β-derivatives is closer to the classical boat form *XXIV* if an intramolecular hydrogen bond cannot be formed; this hydrogen bond stabilizes the form which is closer to the classical boat form *XXV*. The presence of the 8β-methyl group causes the equilibrium to be shifted to the boat form. Introduction of 1α-substituent results in a shift of the equilibrium to the chair form side. By comparison of 1,2 and 2,3-disubstituted derivatives it was established that in the 1,2-series the boat form is less advantageous than in the 2,3-series. The steric nature of these effects is discussed.

In triterpenes and 4,4-dimethyl-5α-steroids which contain an additional substituent in the position 2β it was shown for the series of 2,3-disubstituted derivatives that the ring A exists in boat conformation (see[1-5] and the references therein). The position of the equilibrium of the chair and boat form depends on the nature of the 2β-substituent, on the configuration of the functional group at $C_{(3)}$, on the possibility of forming an intramolecular hydrogen bond, and on the presence of the 8β-methyl group, the effect of which manifests itself by the shift of equilibrium in the direction of the boat form. Analogous 1,2-disubstituted derivatives were studied so far only in the 4,4-dimethyl-5α-cholestane series by Levisalles and coworkers[6] who found the boat form of the ring A in 2β-bromo-1-oxo derivative and partly also in 1α-hydroxy--2β-bromo derivative. In our recent paper[4] we demonstrated that substantial differences exist between 1,2 and 2,3-disubstituted triterpenes (for example in the stereochemistry of the opening of β-epoxides and in the positions of the equilibrium of isomeric 2-bromo ketones), which indicate that in 1,2-disubstituted derivatives the

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boat form of the ring A is less pronounced than in analogous 2,3-isomers. In this paper we investigate the conformation of ring A in bromo ketones and in further derivatives of 19β,28-epoxy-18α-oleanane (I) which contain on $C_{(1)}$ and $C_{(2)}$ bromine,

I
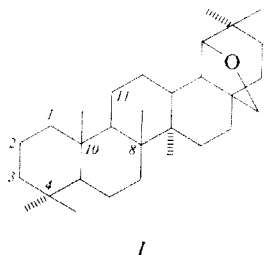
a hydroxyl or an acetoxyl group. Our aim was to determine the preferred conformation of the ring A, and the position of the chair-boat equilibrium, check the effect of the 8β-methyl group in this series of compounds, and determine, by comparison with 2,3-disubstituted derivatives, whether the differences between 1,2 and 2,3-isomers appear generally. For the study we made use of the coupling constants of protons in the ring A, and in the case of hydroxy derivatives also the frequencies and the intensities of the stretching vibrations of the OH bonds. In bromo ketones we also used other methods, giving information on mutual orientation of bromine and the carbonyl group, as for example the frequency of the C=O stretching vibration and the parameters of the $n \rightarrow \pi^*$ transitions in the ultraviolet spectra and in circular dichroism. The preparation of the derivatives $II - XX$ used and the proof of their configuration have already been described[4].

EXPERIMENTAL

The ultraviolet spectra (Table I) were measured on a spectrophotometer Unicam SP 700 in cyclohexane (c 2—5 . 10^{-3} mol l^{-1}) in cells 4 cm thick. Circular dichroism (Table I) was measured on a Roussel-Jouan 185 Dichrographe in dioxan (c 1—1·5 . 10^{-3} mol l^{-1}). The infrared spectra (Table I), carbonyl frequencies, were measured on a UR-20 (Zeiss, Jena) spectrophotometer with a LiF prism, in tetrachloromethane (c 1—2 . 10^{-2} mol l^{-1}) and in KBr cells of 1 mm thickness. The measurements of the OH stretching frequencies (Table II) were carried out on a spectrophotometer Unicam SP 700 with a grating monochromator and in tetrachloromethane (c 1·5—10 . 10^{-3} mol l^{-1}), in infrasil cells 2 or 4 cm thick. For these regions the instruments were calibrated by the spectrum of the atmospheric water vapour; the spectral slit-width was between 2 and 5 cm^{-1}; accuracy of the determination of the band frequencies was 1—2cm^{-1}. The PMR spectra (Table III) were measured at 100 MHz on a Varian HA-100 apparatus at 30°C in deuteriochloroform, pentadeuteriopyridine or in mixtures of deuteriochloroform with hexadeuteriobenzene (Table III) using tetramethylsilane as internal reference. The concentration of the substances was in the 1—3 . 10^{-1} mol l^{-1} range. The multiplets of the protons in positions

1, 2 and 3 were expanded to sweep width 50 or 100 Hz; double resonance experiments were used for their identification. The three-spin systems were analysed in ABX approximation according to[7]. The analysis of four-spin systems in the $C_{(10)}-C_{(1)}$ R^1 $H_Y-C_{(2)}$ R^2 $H_X-C_{(3)}$ H_A $H_B-C_{(4)}$ fragment was carried out under the supposition that $J_{AY} = J_{BY} = 0$, similarly as in paper[5], either as an ABXY system, using the expressions derived by Riggs[8] (method 1 in lit.[5]), or in ABPX approximation according to[9], where the expressions were used for the sum $J_{AX} + J_{BX}$ ($\sum J_{2,3}$) which are generally valid for the ABXY system (method 2 in lit.[5]). In contrast to 2,3-disubstituted derivatives[5] a broadening of the lines was observed in some instances, caused by long-range coupling of 1β and 3β-protons ($|J_{AY}| \leqq 1$ Hz). Ignoring these long-range coupling constants causes in the $\sum J_{2,3}$ value errors lower than 0·1 Hz.

RESULTS AND DISCUSSION

In the case of bromo ketones it is possible, from the values given in Table I, to come to the following conclusions regarding the ring A conformation, making use of the known effects of the axial and the equatorial bromine on the stretching frequency of the carbonyl group[10,11] and the position and the intensity of the $n \rightarrow \pi^*$ transition[12,13]. In 2α-bromo-1-oxo derivative *III* the distinct shift of the carbonyl group absorption $(\varDelta v(CO))$ to higher frequencies, the weak hypsochromic shift $(\varDelta\lambda)$, and the practically unaffected absorption coefficient ε of the $n \rightarrow \pi^*$ transition, as well as the small change in the Cotton effect indicate an equatorial conformation of bromine, which is in agreement with the chair conformation of the ring A. Similarly the values $\varDelta v(CO)$ and $\varDelta\lambda$ in 2β-bromo-1-oxo derivative *IV* exclude the presence of the axial bromine, so that the ring A must exist in boat form. As we were unable to

TABLE I

Characteristic Spectral Parameters of Ketones *II— VII*

Derivative	Substituents	IR Spectra[a]		UV Spectra[b]			Circular dichroism[c]		
		$v(CO)$ cm^{-1}	$\varDelta v(CO)$ cm^{-1}	λ nm	$\varDelta\lambda$ nm	ε 1 . mol^{-1} cm^{-1}	λ nm	$\varDelta\varepsilon$	$\varGamma$ nm
II	1-oxo	1 703	—	297	—	31	311	−0·43	28
							∼275	+0·09	25
III	2α-Br-1-oxo	1 726	+23	291	−6	30	286	+0·77	39
IV	2β-Br-1-oxo	1 724	+21	306	+9	56	300	−1·5	43
V	2-oxo	1 712	—	298[d]	—	23	297[d]	+2·2	39
VI	1α-Br-2-oxo	1 721	+9	311	+13	90	315	−3·2	43
VII	3α-Br-2-oxo	1 713	+1	316[d]	+18	112	316[d]	+8·6	42

[a] In tetrachloromethane; [b] in cyclohexane; [c] in dioxane; [d] the band has a vibrational structure.

TABLE II

Frequencies and Intensities of OH Stretching Vibrations[a]

| Derivative	Substituents		ν(OH) cm^{-1}	$\Delta\nu$(OH) cm^{-1}	$\varepsilon^{(a)}$ l. mol^{-1} cm^{-1}	$\Delta\nu_{1/2}^{(a)}$ cm^{-1}	$B \cdot 10^{-3}$ l. mol^{-1} cm^{-2}
	1	2					
VIII	α-OH	—	f 3 625	—	48	25	1·9
IX	β-OH	—	f 3 619	—	63	14	1·4
X	—	β-OH	f 3 622	—	59	18	1·7
XI	α-OH	β-OH[b]	f 3 625	—	78	27	3·3
			b 3 600	25	35	22	1·2
XII	α-OH	β-Br[b]	f 3 621	4	15	34	0·8
			b 3 587	38	40	22	1·4
XIII	α-Br	β-OH[c]	f 3 622	0	>80	18	>2·3
XIV	α-OH	α-Br	b 3 570	55	56	30	2·4
XV	β-OH	α-Br	b 3 564	55	64	25	2·5
XVI	β-OH	β-Br	b 3 561	58	68	27	2·9

[a] In tetrachloromethane; f free, b bonded, $B = \pi/2$. $\varepsilon^{(a)}$. $\Delta\nu_{1/2}^{(a)}$; $\Delta\nu$(OH) $= \nu_f - \nu_b$ for diol, $\Delta\nu$(OH) $= \nu_{(alcohol)} - \nu_{(bromohydrin)}$ for bromohydrins; [b] after graphical separation; [c] at 1·6 . . 10^{-3} mo l. l^{-1} concentration it has a further band at 3 420 cm^{-1}, $\varepsilon^{(a)} = 20$, concentration dependent.

find any band in the region about $1\,710$ cm^{-1} which corresponded to an axial bromo ketone the content of the chair form at equilibrium is negligible. The coupling constants $J_{2,3\alpha}$ and $J_{2,3\beta}$ (Table III), which correspond in both bromo ketones *III* and *IV* to a diaxial and axial-equatorial conformation of the $C_{(2)}$—H and $C_{(3)}$—H bonds lead to the same conclusion. From Karplus's equation in its simplest form $\left(J = k \cdot \cos^2\varphi \right)$, with the coefficients k found for the fragment —CO—CHBr—CH$_2$— by Abraham and Holker[14], the dihedral angles $\left(\varphi \; 169° \text{ and } 47° \text{ for the 2α-isomer } III,\right.$ φ 48° and 169° for the 2β-isomer *IV*)* were calculated, which correspond to the chair form of the ring A in bromo ketone *III* and the boat form in bromo ketone *IV*. Although the φ values are only approximate (the effect of the orientation of the electronegative substituent[15,16] is not considered), the agreement of φ and $J_{2,3}$ in bromo ketones *III* and *IV* indicates that the dihedral angles of the C—H bonds in the positions 2 and 3 are approximately equal in the chair and the boat form. The true geometry of the boat form of the 2β-bromo ketone *IV* will lie between the two possible classical forms *XXI* and *XXII* with $C_{(3)}$ and $C_{(10)}$ or $C_{(2)}$ and $C_{(5)}$ in stem-stern

* These angles differ appreciably from those given for analogous bromo ketones derived from 4,4-dimethyl-5α-cholestane[6]. The differences are probably due to the using of the first-order coupling constants for the calculations in paper[6].

positions. The dihedral angle of the C—Br and C=O bonds differs in both extreme forms: in the form *XXI* it is about 60°, while in the form *XXII* both bonds are practically coplanar. The bathochromic shift $(\Delta\lambda + 9$ nm$)$, the increase of the absorption coefficient ε and the relatively low shift of $\Delta\nu(CO)$ in 2β-bromo-1-oxo derivative *IV* $\left(+21 \text{ cm}^{-1}\right.$, in comparison with the value $+26 \text{ cm}^{-1}$ found in 2β-bromo-3-oxo derivative in the boat form[17]$)$ indicate that in bromo ketone *IV* bromine has a less equatorial character, and that, therefore, the energy minimum of the boat form is not close to the form *XXII*, but that it corresponds rather to the twist form, or that it is closer to the form *XXI*. Further, the comparison of the circular dichroism (which is very sensitive to geometry changes) of ketones *II−IV* and analogous derivatives of 4,4-dimethyl-5α-cholestane derivatives[6] is interesting: in unsubstituted 1-oxo derivatives and in 2α-bromo-1-oxo derivatives the $\Delta\varepsilon$ values in both series agree, which means that the effect of the 8β-methyl group (or also the rest of the skeleton, in which both series differ) on the Cotton effect is small and that the conformations of the ring A are similar. In contrast to this, in 2β-bromo-1-oxo derivatives the differences are significant; in derivative *IV* the Cotton effect is less negative $\left(\Delta\varepsilon \; -1\cdot5\right)$ than in 2β-bromo-4,4-dimethyl-5α-cholestan-1-one $\left(\Delta\varepsilon \; - \; 3\cdot24\right)$. The Cotton effect is determined here rather by the chirality of the boat form of the ring A than by the bromine atom. Hence, this difference indicates that the geometry of the boat form is in both 2β-bromo ketones different, which would also explain the discrepancies in the positions of the isomerization equilibria of 2-bromo ketones, discussed in greater detail in paper[4].

The spectral data of 2-oxo derivatives *VI* and *VII* correspond to axial bromo ketones with the ring A in chair form. The sign of the Cotton effect of 1α-bromo ketone *VI* is opposite to that in 3α-bromo ketone *VII*, as may be expected according to the octant

XXI   *XXII*

XXIII   *XXIV*   *XXV*
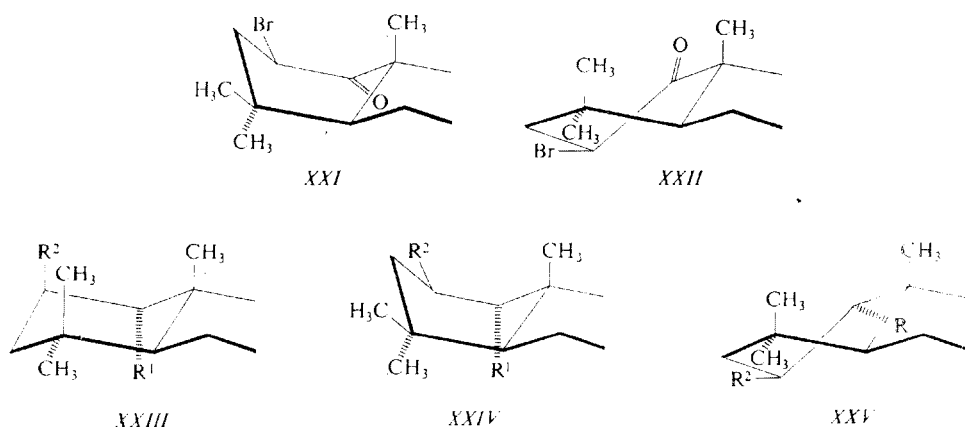
R^1, R^2 = Br, OH, OAc

TABLE III
Coupling Constants and Chemical Shifts of Protons in Ring A

| Deri-vative | Substituents | | Solvent | $J_{1,2}$ | $\sum J_{2,3}$ | $J_{2,3\alpha}$ | $J_{2,3\beta}$ | $-J_{3\alpha,3\beta}$ | δ_{1H} | δ_{2H} | $\delta_{3\alpha H}$ | $\delta_{3\beta H}$ | Method of analysis[a,b] |
	1	2											
III	=O	α-Br	CDCl$_3$	—	19·6	13·8	5·8	13·0	—	5·38	2·01	3·37	ABX
IV	=O	β-Br	CDCl$_3$	—	19·9	~5·8[c]	~14·1[c]	13·6	—	4·84	2·20	2·25	ABX
			C$_6$D$_6$	—	19·4	5·6	13·8	13·8	—	4·41	1·98	2·18	ABX
XI	α-OH	β-OH	C$_5$D$_5$N[d]	3·4	8·6	(4·4)	(4·2)	13·6	3·91	4·38	(1·78)	(2·01)	ABPX
XVII	α-OAc	β-OAc	CDCl$_3$	3·4	9·4	~4·7	~4·7	e.f	4·81	4·91	e	e	ABXY
XII	α-OH	β-Br[g]	CDCl$_3$	~6·6	~18·4	~4·8	~13·6	e	~3·80	~4·10	e	e	first-order
			C$_5$D$_5$N[d]	6·0	17·8	4·7	13·1	14·0	3·95	4·46	1·87	2·13	ABPX
XVIII	α-OAc	β-Br	CDCl$_3$	6·0	17·5	~4·7	~12·8	~14	5·14	4·10	~1·89	~2·18	ABPX
XIII	α-Br	β-OH	CDCl$_3$	2·8	8·6	e	e	e.f	4·28	4·46	e	e	ABXY
XIX	α-Br	β-OAc	CDCl$_3$	~2·5	6·8	(~4·3)	(~2·5)	e.f	4·30	5·41	e	e	ABPX
XX	α-Br	β-Br	CDCl$_3$	4·5	14·2	e	e	e	4·57	4·82	~2·13	~2·13	ABPX
			CDCl$_3$ + C$_6$D$_6$ 1:1	4·4	14·3	~4	~10	~13·5	4·53	4·80	~2·03	~2·00	ABPX
XIV	α-OH	α-Br	CDCl$_3$	2·0	17·6	13·3	4·3	~13	~3·68	4·85	~2·13	~1·71	ABPX
			CDCl$_3$ + C$_6$D$_6$ 1:1	2·1	17·7	13·3	4·4	~13	~3·58	4·71	~2·13	~1·63	ABPX
XV	β-OH	α-Br	CDCl$_3$	9·5	17·9	~13·5	~4·4	~13	3·38	4·38	~1·90	~2·07	ABPX
XVI	β-OH	β-Br	CDCl$_3$	4·6	17·0	2·9	14·1	13·5	~3·48	4·56	<1·60	~2·21	ABPX
			CDCl$_3$ + C$_6$D$_6$ 1:1	4·7	16·8	2·9	13·9	~13·5	~3·39	4·39	~1·53	~2·17	ABPX

[a] Chemical shifts in δ-scale (p.p.m.), rounded up to 0·01 p.p.m., accuracy ±0·005 p.p.m.; coupling constants in Hz, accuracy ±0·2 Hz; the values in parentheses are assigned tentatively and they may be mutually interchanged; [b] see Experimental; [c] low accuracy is caused by the degeneration of the AB part; [d] with a trace of CD$_3$COOD; [e] indeterminable values; [f] $|J_{1\beta,3\beta}| \leqq 1$ Hz; [g] the low accuracy is caused by low solubility and the overlapping of the signals of 1β-H and C$_{(28)}$-H$_2$.

rule. From the comparison of isomers *VI* and *VII* it is further evident that the intro-
duction of bromine into the position 1α causes a higher shift in $\Delta v(CO)$, a lower shift
of $\Delta\lambda$, a lower increase in ε, and a smaller change of the Cotton effect than the intro-
duction of bromine into the position 3α. Hence, it seems that 1α-bromine has a less
pronounced axial character than 3α-bromine; this may mean either a general effect,
given by the deformation of the ring A in triterpenes, or the phenomenon might be
caused by differences in the interactions of 1α- and 3α-bromine with the hydrogen
atoms.

   In compounds which do not have a carbonyl group in the ring A, we used, similarly
as in lit.[5], for the study of the ring A conformation the spectral shifts of the bonded
hydroxyl in the infrared spectra $(\Delta v(OH)$, Table II) and the values of the vicinal
coupling constants $J_{1,2}$, $J_{2,3\alpha}$ and $J_{2,3\beta}$, and also the sum of the latter two constants
$(\sum J_{2,3}$; Table III). In derivatives containing the 2α-substituent, *i.e.* in *trans*-bromo-
hydrin *XV* and *cis*-bromohydrin *XIV*, these parameters are in agreement with the
chair form of ring A and the diequatorial or axial-equatorial arrangement of the
substituents. In derivatives containing a 2β-substituent the chair form *XXIII* is
destabilized by 1,3-*syn*-axial interactions between the 2β-substituent (R^2) and the
4β and 10β-methyl groups, so that it is necessary to consider the possibility of the
existence of ring A in the boat form. For the differentiation of both forms in 1α,2β-
-derivatives and for the determination of their ratio $J_{1,2}$ cannot be used unless the
geometry of the boat form in each of the derivatives is known beforehand. This
coupling constant is very sensitive to the geometry of the boat form and it can be
changed within a broad range in dependence on the dihedral angle of the C—H
bonds, which, according to molecular models, is close to 120° in the classical boat
form *XXIV*, and to 180° in the form *XXV*. In contrast to this $J_{1,2}$ is suitable for an
estimation of whether the true geometry of the boat form represents a centre of pseu-
dorotation between the forms *XXIV* and *XXV*, or whether it is closer to one of them.
As the dihedral angles between the hydrogens in the positions 2 and 3 change only
negligibly during the pseudorotation of the boat form, and because the dihedral angle
between 2α-H and 3β-H differs substantially in the boat and the chair form, $J_{2,3\beta}$
or $\sum J_{2,3}$ may be used for the differentiation of both forms in 1α,2β- and in 1β,2β-
-derivatives. In 2β-hydroxy and acetoxy derivatives *XI*, *XIII*, *XVII* and *XIX* these
values do not differ too much from those expected for the chair form *XXIII*, but in
2β-bromo derivatives *XII*, *XVI*, *XVIII* and *XX* they are much higher, which corres-
ponds to a distinct presence of the boat form.

   We tried to calculate the population of the boat form of the ring A from the ob-
served $\sum J_{2,3}$ values (which could always be obtained from the spectrum with
sufficient accuracy) and $J_{2,3\beta}$ values in the same manner as in 2,3-disubstituted deri-
vatives[5]. For the finding of the starting values of „pure" chair and boat form we made
use of four methods (A, B, C, D). The structural model for the methods *A*, *B* and *C*
is cyclohexane; while in method *A* the effect of substituents is completely neglected,

in method B the values $J_{2,3}$ are corrected to the electronegativity of the substituents, and in method C the magnitude of the contributions of electronegative substituents is also differentiated in dependence on the orientation with respect to the C—H bonds. A more detailed description of these methods and the dihedral angles* used are given in paper[5]. In method D the data found experimentally in suitable steroidal and tri-terpenoid models are used as starting values for coupling constants, and the differences in electronegativities of substituents are neglected. For the chair form we adopted the values employed in paper[5]: $J_{2,3\beta} = 3\,\text{Hz}$, $\sum J_{2,3} = 7$ Hz. For the boat form we could not find a suitable model, because up to now no 1,2-disubstituted derivative is known for which it would be proved by an independent method that it existed in boat form. Therefore, we made use of the fact (see above) that in the boat form of 2β-bromo ketone IV the same values of coupling constants $J_{2,3}$ were found as in the chair form of 2α-bromo ketone III, and we chose as models 1,2-disubstituted derivatives XIV and XV which contain 2α-bromine and have their ring A in chair form. For the boat form we used then $J_{2,3\beta} = 13\cdot4$ Hz and $\sum J_{2,3} = 17\cdot7$ Hz, which are the averages of the values $J_{2,3\alpha}$ and $\sum J_{2,3}$ found in 1α-hydroxy-2α-bromo derivative XIV and 1β-hydroxy-2α-bromo derivative XV.

The populations of the boat form of ring A in 1,2-disubstituted derivatives, obtained by methods A, B, C and D both from $J_{2,3\beta}$ and from $\sum J_{2,3}$ are given in Table IV. The mutual agreement of single values is somewhat worse than in 2,3-isomers[5], which may be caused by the low accuracy of the determination of the experimental value $J_{2,3\beta}$ from the spectra and also by the fact that two coupling constants must be calculated to obtain the starting values $\sum J_{2,3}$ by the methods A, B and C, so that in the calculation of the population a further possible error in $J_{2,3\alpha}$ is included in addition to the error in $J_{2,3\beta}$. In addition to this a systematic error is also included in the calculations, which manifests itself most in 2β-bromo derivatives XII and XVI by the fact that the obtained values for the population of the boat form exceed 100%. This means that the „true" values of $J_{2,3\beta}$ and $\sum J_{2,3}$ are for the boat form of 1,2--disubstituted derivatives higher than the structural models used in methods A, B, C and D permit. This may be partly caused by the different geometry of the boat form in 1,2-isomers. However, as the found values of $J_{2,3\beta}$ are higher than the maximum values which may be obtained from the relations used[5] $J = f(\varphi)$, other factors are probably involved which affect the magnitude of J (for example the effect of the electronegative substituent on the neighbouring carbon atom[16], or the effect of its orientation — see bromohydrins XII and XVI in Table III). In Table IV are further given the mean values for the population of the boat form of 1,2-disubstituted derivatives (averages of values obtained by all methods) and for the sake of comparison also the mean values of the population for analogous 2,3-isomers, taken from paper[5].

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* The values of $\varphi_{1\beta,2\alpha}$ were given erroneously in paper[5]. For classical boat forms 118° and 175° and for twist form 146·5° were used in reality in methods A, B and C.

TABLE IV

Population of the Boat Form of the Ring A (in %) in 1,2 and 2,3-Disubstituted Derivatives of 19β,28-Epoxy-18α-oleanane (I)

| Derivative | Substituents | | Solvent | 1,2-Series | | | | | | | | | 2,3-Series mean value[b] |
| | 1 | 2 | | from $J_{2,3\beta}$ by method | | | | from $\sum J_{2,3}$ by method | | | | mean value[a] | |
				A	B	C	D	A	B	C	D		
XI	α-OH	β-OH	C_5D_5N	12	15	9	12	20	26	31	15	18	64
XVII	α-OAc	β-OAc	$CDCl_3$	17	21	15	16	27	34	38	22	24	59
XII	α-OH	β-Br	$CDCl_3$	105	110	110	102	116	123	116	107	100	99
XII	α-OH	β-Br	C_5D_5N	100	104	105	97	110	117	110	101	100	95
XVIII	α-OAc	β-Br	$CDCl_3$	97	101	101	94	107	113	108	98	100	100
XIII	α-Br	β-OH	$CDCl_3$	—	—	—	—	20	26	31	15	23	88[c]
XIX	α-Br	β-OAc	$CDCl_3$	−5	−3	−7	−5	2	7	15	−3	0	54
XX	α-Br	β-Br	$CDCl_3$	—	—	—	—	75	80	77	67	75	—
XX	α-Br	β-Br	$CDCl_3 + C_6D_6$ 1:1	69	73	72	67	76	81	78	68	73	70[d]
XVI	β-OH	β-Br	$CDCl_3$	110	115	115	107	102	108	104	93	100	58
	β-OH	β-Br	$CDCl_3 + C_6D_6$ 1:1	108	113	113	105	100	106	102	92	100	60

[a] The arithmetic mean of all values given; if the average is higher than 100% the value 100% is given; [b] taken from lit.[5] for 2,3-disubstituted derivatives which differ from the 1,2-series by the fact that the substituent mentioned for the position 1 is in the position 3; [c] 46% in C_5D_5N; [d] in C_6H_6.

In view of the systematic error discussed the true values for the population of the boat form in 1,2-isomers are rather slightly lower than the mentioned mean values.

According to these results 1α-hydroxy-2β-bromo derivative *XII* and 1α-acetoxy-2β-bromo derivative *XVIII* have the ring A practically completely in the boat form. From the value $J_{1,2} = 6$ Hz, found in bromohydrin *XII* (in C_5D_5N) and acetate *XVIII* it is now possible to determine the dihedral angle φ between 1β-H and 2αH, and thus determine the geometry of the boat form under the supposition that a single minimum of potential energy exists between the classical forms *XXIV* and *XXV*. We consider that this assumption is justified if the formation of the intramolecular hydrogen bond is prevented (by acetylation or by measurement in pyridine); cases when the hydrogen bond is present in the boat form are discussed further in connection with infrared spectra. The use of various relationships $J = f(\varphi)$ (for example methods *A* and *B* according to lit.[5], general relationships according to Pachler[15], the relation $J = k \cdot \cos^2\varphi$ in which k was considered within the $11-14$ Hz range) leads to practically identical value of φ, within the limits $135 \pm 4°$. This means that the geometry of the boat form of $1\alpha,2\beta$-derivatives does not correspond to the twist form, representing the centre of pseudorotation between the classical forms *XXIV* and *XXV* ($\varphi \sim 150°$), but it is closer to the classical boat form *XXIV* with $C_{(3)}$ and $C_{(10)}$ in stem-stern positions ($\varphi \sim 120°$). This is evidently a consequence of the interaction between the 4β and 10β-methyl groups, that occurs in the form *XXV*, but not in the form *XXIV*.

The use of infrared spectra in the region of OH stretching frequencies for the study of ring A conformation is more complex in the case of *trans*-bromohydrins and diols of $1\alpha,2\beta$-configuration than in analogous 2,3-isomers[5]. In this case the bands of the free and the bonded hydroxyl cannot be assigned unambiguously to the boat or the chair form. In the chair form of *XXIII* the formation of the intramolecular hydrogen bond is impossible; in the boat form the dihedral angle Θ between the substituents taking part in the hydrogen bond can change in dependence on the geometry of the boat form ($60° < \Theta < 120°$). At $\Theta \sim 120°$ the hydrogen bond is generally not formed according to literature[18,19]; at $\Theta \sim 90°$ a weak hydrogen bond has already been observed ($\Delta v(\text{OH}) = 18 \text{ cm}^{-1}$) in amino alcohols derived from twistane[19]. However, as in amino alcohols $\Delta v(\text{OH})$ are several times higher than in bromohydrins and diols[18], it cannot be expected that a band of bonded hydroxyl could be observed in $1\alpha,2\beta$-derivatives when the geometry of the boat form is closer to the form *XXIV* ($90° < \Theta < 120°$), *i.e.* similar to the form determined from PMR spectra. On the contrary, if it is closer to the form *XXV* ($60° < \Theta < 90°$) the hydrogen bond is possible and in an extreme case $\Delta v(\text{OH})$ can attain values found in diequatorial derivatives in chair form. Hence, the band of the intramolecularly bonded hydroxyl indicates the boat form, but its absence does not exclude it. A weak band at $3\,600 \text{ cm}^{-1}$ in the spectrum of $1\alpha,2\beta$-diol *XI* lies outside the region in which the rotamers of the C—OH bonds of non-bonded hydroxyl groups[20] occur; therefore, we assign it to the

bonded hydroxyl in boat form. The value $\Delta v(OH)$ $(25\ \text{cm}^{-1})$ is lower than in diequatorial $2\alpha,3\beta$-diol $(37\ \text{cm}^{-1}$, see[5]), which corresponds to the fact that the boat form is considerably — but not completely — turned to the side of the form XXV. If the values of integrated intensities B of the free and the bonded hydroxyl of 2,3-diols are taken into account in which the formation of the hydrogen bond is practically complete $(B_f \sim 1\,800,\ B_b \sim 3\,800$, see[5]), it can be estimated from the data B_f and B_b in $1\alpha,2\beta$-diol XI (Table II) that the content of the boat form of this geometry is about 30%. The remaining 70% may be either in chair form or in boat form of a different geometry.

In the spectrum of 1α-hydroxy-2β-bromo derivative XII two bands appear: the intensive band of the bonded hydroxyl indicates that the boat form of similar geometry as in diol XI predominates. The shift $\Delta v(OH) = 38\ \text{cm}^{-1}$ is again smaller than in the diequatorial bromohydrin XV $(55\ \text{cm}^{-1})$. The second band $(\Delta v(OH) = 4\ \text{cm}^{-1})$ corresponds to the form with a free hydroxyl; from the ratio B_f/B_b we calculated — in the same manner as in lit.[5] — that the content of the form with a free hydroxyl is $36 \pm 10\%$. As according to the PMR spectra the ring A of bromohydrin XII exists practically in the boat form only (in $CDCl_3$ and in C_5D_5N where the boat form is not stabilized by a hydrogen bond), it is impossible that such a high content of the form with a free hydroxyl would be caused by the chair form $XXIII$. Therefore we consider that two different boat forms take part in equilibrium, which differ by the geometry of ring A: the form stabilized by the hydrogen bond is closer to the form XXV $(\sim 64\%)$, and the second form, with the free hydroxyl, is closer to the form $XXIV$ $(\sim 36\%)$.*

This means that during the pseudorotation of the boat form between the extreme forms $XXIV$ and XXV two minima of potential energy exist. For the formation of the energy barrier between them the simultaneous action of two opposite effects may mainly contribute (in addition to the rotation barrier for the C—OH bond, if the rotamers participate at all), which become most manifest in the form XXV: one of them is the repulsion between the 4β and 10β-methyl groups, the second is the intramolecular hydrogen bond which has the character of an attraction. The bromohydrin XII evidently represents one of the few compounds in which this unusual phenomenon

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* In this form various rotamers of the C—OH bond with the hydroxyl group turned away from bromine may be also populated, but the possibility that the band of the free hydroxyl is caused by these rotamers only (without a change in the geometry of the ring) seems unlikely. In bromohydrins in which the formation of the hydrogen bond is enabled by the ring A geometry the rotamers taking part in the hydrogen bond are much more stable than the rotamers which are turned away; in these bromohydrins we did not observe the band of the free hydroxyl either in the 1,2-series or in 2,3-series[5]. It is true that it was detected in some steroidal halohydrins, but only of low intensity[21]. In addition to this it may be expected that the abolishment of the stabilization energy of the hydrogen bond (in the averted rotamer) should also result in a change in the geometry of the boat form in the direction of the form $XXIV$ (i.e. to the form determined from the PMR spectra in derivatives which do not form a hydrogen bond, see above).

may be observed; unfortunately, its more detailed study was hampered by the negligible solubility of bromohydrin *XII* in non-polar solvents. The conclusions regarding the geometry of the boat form of ring A in 1α, 2β-disubstituted derivatives, obtained from the infrared and PMR spectra, may be summarized as follows: unless an intramolecular hydrogen bond is possible between the groups R^1 and R^2 the geometry is closer to the form *XXIV*; the hydrogen bond stabilizes the form which is closer to the form *XXV*.

The behaviour of 1α-bromo-2β-hydroxy derivative *XIII* is also worth mentioning; in its infrared spectrum in addition to the band of the free hydroxyl a relatively intensive broad band at $3420\ cm^{-1}$ also appears even at concentration $1\cdot6 \cdot 10^{-3}\ mol\ l^{-1}$, which is caused by the intermolecular hydrogen bond, as the intensity of both bands changes characteristically with concentration. The reason for such a high tendency to association just in isomer *XIII* is not clear; we could not detect a similar phenomenon in any of the bromohydrins or alcohols mentioned here or in paper[5], even at substantially higher concentrations (in some instances higher even by one order of magnitude). In $1\alpha,2\beta$-diol *XI*, which is the closest analogue of bromohydrin *XIII*, we also did not observe association at the $2\cdot10^{-3}\ mol\ l^{-1}$ concentration; in concentration $4\cdot10^{-3}$ $mol\ l^{-1}$ a weak band of the intermolecularly bonded hydroxyl already appears.

Although the mean values of the populations of the boat form of ring A, shown in Table IV, represent only approximate estimations, the subsequent effects of substituents on the ring A conformation are so important that they are clearly evident even from the comparison of these data.

1) If bromine is in the position 2β $(R^2 = Br)$ the equilibrium in 1α, 2β and in $1\beta,2\beta$-disubstituted derivatives is shifted far to the boat form side. In contrast to this, if the 2β-substituent is an oxygen-containing function $(R^2 = OH,\ OCOCH_3)$ the chair form strongly prevails. The difference between the effect of bromine and oxygen, expressed as a difference in the values ΔG° of the chair-boat equilibrium, is approximately 2 kcal . mol^{-1}. When considering all non-bonding interactions that appear in the chair and in the boat form of 1,2-disubstituted derivatives, it may be concluded that this difference is caused predominantly by two 1,3-*syn*-axial interactions of the 2β-substituent with the methyl groups in the chair form of the ring A. This represents a further corroboration of the conclusion made on the basis of 2,3-disubstituted derivatives[5], *i.e.* that 1,3-*syn*-axial interaction CH$_3$/Br is at least 0·5 kcal . mol^{-1} higher than the interaction CH$_3$/OH or CH$_3$/OCOCH$_3$.

2) From the first-order coupling constants, published[6] for 2β-bromo-4,4-dimethyl-5α-cholestan-1α-ol $(J_{1,2} = 6\ Hz,\ \sum J_{2,3} \sim 15\ Hz)$, it may be estimated that the content of the boat form at equilibrium is higher than 70% and in its acetyl derivative $(J_{1,2} = 3\cdot5\ Hz,\ \sum J_{2,3} \sim 11\ Hz)$ lower than 40%. If these values are compared with the data for derivatives *XII* and *XVIII*, it is evident that in triterpene derivatives containing 8β-methyl group the content of the boat form is higher than in 4,4-dimethyl-$5\text{-}\alpha$-cholestane derivatives. The effect of the 8β-methyl group here causes a shift of the equilibrium towards the boat form, similarly as in 2,3-disubstituted derivatives[5].

3) From the comparison of 1α,2β-derivatives containing a hydroxyl group in the position 2β (*XI, XVII, XIII, XIX*) with analogous 2,3-isomers it follows that in the 1,2-series the equilibrium is shifted more in the direction of the chair form than in the 2,3-series. In *trans*-bromohydrins and their acetates, containing a 2β-bromine, this effect cannot be observed because the equilibrium is shifted in both series too far to the boat form side. However, it appears in 2β-bromo derivatives of 4,4-dimethyl--5α-cholestane[3,6]: in 1α-acetoxy-2β-bromo derivative the chair form prevails (less than 40% of the boat form; see above), in 2β-bromo-3α-acetoxy derivative it is the boat form which predominates (more than 70%; see[5]). An exception from this rule are *trans*-dibromo derivatives: in 1α,2β-dibromo derivative *XX* the position of the equilibrium is approximately equal as in 2β,3α-isomer. Here the repulsion between the dipoles of the C—Br bonds evidently plays a role (see also[5,22]); it destabilizes the boat form of 2β,3α-dibromo derivative more ($\Theta < 60°$) than in 1α,2β-isomer *XX* ($\Theta > 90°$). A further exception are *cis*-bromohydrins: in 1β-hydroxy-2β-bromo derivative *XVI* the boat form predominates highly, while in 2β-bromo-3β-hydroxy derivative both forms are present in comparable amounts. In this case, however, the boat form of the 2β,3β-isomer is destabilized by the strong interaction between the 3β--hydroxyl and 10β-methyl group, as was found quite independently on the basis of comparison of 2,3-disubstituted derivatives[5]. A similar interaction does not occur in the boat form of 1β-hydroxy-2β-bromo derivative *XVI*: on the contrary, the interaction between the 1β-hydroxyl group and the 11α-hydrogen in the chair form of derivative *XVI* may by reduced in the boat form. Hence, it may be concluded that the ring A of 1,2-disubstituted derivatives has a lower tendency to assume the boat conformation than in 2,3-isomers unless further factors destabilizing the boat form are involved.

The differences between the 1,2 and 2,3-derivatives are significant: if expressed as differences in the values $\Delta G°$ of the chair–boat equilibrium it may be estimated from the values in Table IV that they are close to 1 kcal . mol^{-1}. Data used for the estimation were obtained under the conditions when an intramolecular hydrogen bond does not form, so that these values would not be affected by the differences in stabilization energies of the hydrogen bond in the boat form of both series. We observed the same effect earlier[4] in the stereochemistry of the opening of β-epoxides with hydrobromic acid and in the positions of the isomerization equilibria of 2-bromo-1-oxo and 2-bromo-3-oxo derivatives. For the difference between 1,2 and 2,3-isomers we have found in the first case the value 1·4 kcal . mol^{-1} (from $\Delta G^{\neq}$ of the chair and the boat transition state) and in the second 1·2 kcal . mol^{-1} (from $\Delta G°$ of the equilibrium of 2α- and 2β-bromo ketones which have the ring A in the chair or the boat form, respectively). Qualitatively the same effect appears in the reactions of *cis*-bromohydrins in alkaline medium[4]: 2α-bromo-3α-hydroxy derivative reacts in the boat form and gives on elimination of *anti*-periplanar substituents (Br, H) a ketone, while 1α-hydroxy-2α-bromo derivative reacts in the chair form under contraction of ring A.

Hence, it seems that the mentioned effect appears quite generally, both in conformational equilibria and during the reaction course. The difference between the positions 1 and 3 also appears during the following comparison: In paper[5] we found that 2β-hydroxy derivative X and its acetyl derivative have their ring A partly in the boat form ($\sim 60\%$ or $\sim 40\%$, resp.). We have further observed that the introduction of the 3α-substituent (Br, OH, OCOCH$_3$) does not practically affect the position of the chair–boat equilibrium. As may be seen from the values given in Table IV, the introduction of the same substituents into position 1α has, on the contrary, a significant effect on the position of the equilibrium and causes in all instances a shift in the direction of the chair form. These differences are probably not caused by the chair form, because the non-bonding interactions of the 1α and 3α-substituents in it do not practically differ. Hence, the nature of the effect will consist rather in energy relationships in the boat form; we came to the same conclusion also from the stereochemistry of the opening of β-epoxides[4].

The reasons for a lower stability of the boat form of 1,2-disubstituted derivatives in comparison with 2,3-isomers are not clear. In terms of the usual non-bonding interactions we could not find any simple and general explanation which would be utilizable for all phenomena observed (conformational equilibria of *trans*-derivatives, isomerization equilibria of bromo ketones, opening of β-epoxides, and reactions of *cis*-bromohydrins). Although we cannot exclude that it is a chance agreement, and that in each of the mentioned cases other interactions are decisive, we consider that in all instances the asymmetry of the boat form of the ring A plays an important role (*i.e.* the asymmetric arrangement of the substituents in the position 1 and 3 with respect to $C_{(2)}$). In other words, in the boat form the bonds $C_{(1)}$—$C_{(2)}$ and $C_{(2)}$—$C_{(3)}$ are each of a different type: the first is characterized by an internal torsion angle between $0°$ and $60°$ ($\sim 30°$ according to[23]), the second by an angle $\sim 65°$. It is possible that in derivatives which contain two polar substituents the first type is energetically less advantageous. At present it is difficult to decide whether this effect is limited to disubstituted steroid and triterpene derivatives, or whether it is general at least for substances containing a six-membered ring connected with a rigid skeleton (especially problematic is the question to what extent the energy of the chair and the boat form of the ring A is affected by the interaction of various substituents on $C_{(1)}$ with the 11-methylene group). In literature we were unable to find a single case where a similar effect was observed, and no experimental data were found either, which could contribute to its elucidation. Theoretical calculations of conformational energies for various pseudorotational arrangements of the boat form were carried out in unsubstituted cyclohexanone only[24−26]; according to the results obtained by the force field method[25,26] the arrangement with the symmetry C_2 (pseudorotational parameter $90°$, see [24]) is energetically more favourable than other arrangements of the boat form of cyclohexanone of symmetries C_s or C_1 (pseudorotational parameter $0°$, $30°$ or $60°$). As in triterpene 1-oxo derivatives the boat form of the ring A

corresponds to the first arrangement, while in 3-oxo derivatives to the second one, it should be more preferred in the 1-oxo series than in the 3-oxo series. This does not agree with the results obtained on the basis of isomerizations of bromo ketones, where we observed the opposite effect[4].

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