

THE EFFECT OF 8 β -METHYL GROUP ON THE CONFORMATION OF THE RING A OF 2,3-DISUBSTITUTED TRITERPENES*

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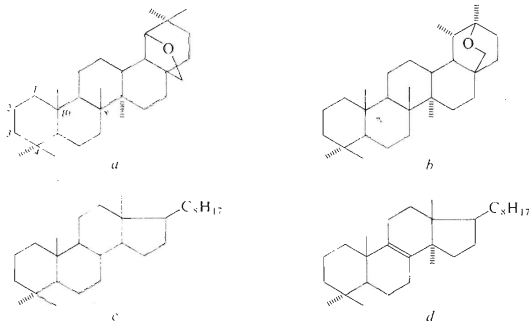
The conformation of the ring A in 2,3-disubstituted derivatives of 19 β ,28-epoxy-18 α -oleanane (a) — diols, bromohydrins, their acetates and dibromo derivatives — was studied on the basis of the stretching vibrations of OH bonds as well as of the vicinal coupling constants obtained by a complete analysis of the ABXY system of protons in ring A. In derivatives of 2 β ,3 α -configuration which contain a 2 β bromine atom the ring A is in the boat form, while in derivatives which contain a 2 β -hydroxyl (or acetoxy) the boat and the chair forms are at equilibrium present in approximately equal amounts unless the boat form is stabilized by an intramolecular hydrogen bond. The formation of a hydrogen bond causes a shift in equilibrium towards the boat form, while the change in configuration at the position 3 (2 β ,3 β -derivatives) produces a shift to the chair form. The magnitude of 1,3-*syn*-axial interactions CH₃/Br and CH₃/OH is also discussed. By comparison with 4,4-dimethyl-5 α -steroids it was inferred that the presence of the 8 β -methyl group in triterpenes significantly affects the conformation of ring A and that in all instances it is manifested by a shift in equilibrium towards the boat form.

Non-bonding 1,3-*syn*-axial interactions between 4 β and 10 β -methyl groups and another substituent in the position 2 β in the chair form of the ring A of 4,4-dimethylsteroids and triterpenes** can destabilize this form to such an extent as to cause the ring A to exist predominantly, or at least partly, in boat form in which the mentioned interactions disappear^{1,2}. In the series of 2,3-disubstituted derivatives this phenomenon is well known in 2 β -bromo-3-ketones. Both in 4,4-dimethylsteroids and in triterpenes of this type it was observed that the ring A exists practically in the boat form³⁻⁶ only. A similar situation exists also in 2 β -bromo-3 α -hydroxy derivatives⁵⁻⁸, while in isomeric 2 β -hydroxy-3 α -bromo derivatives of 4,4-dimethylsteroids an equilibrium between the chair and the boat form was observed⁶⁻⁸. The boat form was also observed in triterpenic 2 β ,3 α -diols^{9,10}. In contrast to 4,4-dimethylsteroids an additional axial methyl group in the position 8 β is present in triterpenes, which interacts sterically with 10 β -methyl group, and can therefore also affect the conformation of the ring A.

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** Under the concept "triterpenes" those triterpenes are meant in this paper which contain a 8 β -methyl group in addition to 4 α , 4 β and 10 β -methyl groups. Among 4,4-dimethylsteroids those tetracyclic triterpenes are counted that do not contain a 8 β -methyl group. In both cases they are derivatives with a 5 α -configuration.

In our previous papers^{5,11} we have demonstrated that differences may be detected between the triterpenic and 4,4-dimethylsteroid series with respect to the opening of 2 β ,3 β -epoxides and the isomerizations of 2-bromo-3-ketones; these differences may be assigned to the effect of 8 β -methyl group: in derivatives of 19 β ,28-epoxy-18 α -oleanane (*a*) and 20 β ,28-epoxy-18 α ,19 β *H*-ursane (*b*) the boat form of ring A (or the boat-like transition state) is more preferred than in analogous derivatives of 4,4-dimethyl-5 α -cholestane (*c*) and 8-lanostene (*d*). If this "8 β -methyl effect" is general,



it may be expected that it will manifest itself in the same manner not only in reactions, but also in the positions of the equilibria of the chair and boat forms of ring A in derivatives containing a 2 β -substituent. In this paper we therefore studied the conformations of ring A in 2,3-disubstituted triterpenes — diols, bromohydrins, and their acetates and dibromo derivatives derived from the skeleton *a* or *b* — with the following aims: 1) to determine the preferred conformation of the ring A in dependence on the type and the configuration of substituents; 2) to determine the ratio of the chair and boat forms in cases when the population of both forms is significant; 3) to determine the effect of the 8 β -methyl group on the position of the equilibrium by comparison of the results with the data published⁶⁻⁸ for analogous 4,4-dimethylsteroid derivatives of series *c* and *d*. For this purpose we made use of the vicinal coupling constants of protons in the positions 1, 2 and 3, obtained from the PMR spectra, and in the case of hydroxy derivatives also of the frequencies and intensities of the stretching vibrations of OH bonds in infrared spectra. The stereospecific preparation of the derivatives *I*–*XVII* used, derived from skeletons *a* and *b*, and the confirmation of their configuration by chemical means is described in our earlier communications^{5,11-13}.

TABLE I
Frequencies and Intensities of OH Stretching Vibrations^a

Compound	Substituents in position		ν cm ⁻¹	$\Delta\nu$ cm ⁻¹	$\epsilon^{(a)}$ l mol ⁻¹ .cm ⁻¹	$\Delta\nu_{1/2}^{(a)}$ cm ⁻¹	$B \cdot 10^{-3}$ l mol ⁻¹ .cm ⁻²
	2	3					
<i>Ia</i>	β -OH	—	f 3 622	—	59	18	1.7
<i>IIa</i>	α -OH	—	f 3 620	—	40	24	1.5
<i>IIIa</i>	—	β -OH	f 3 633 f 3 625sh	—	44	25	1.7
<i>IVa</i>	—	α -OH	f 3 638	—	55	21	1.8
<i>Va</i>	β -OH	α -OH ^b	f 3 634 b 3 594	— 40	52 52	23 47	1.9 3.8
<i>VIa</i>	α -OH	β -OH ^b	f 3 633 b 3 596	— 37	46 76	25 32	1.8 3.8
<i>VIIa</i>	β -OH	α -Br ^b	f 3 620 b 3 571	2 51	14 51	16 25	0.35 2.0
<i>VIIIa</i>	β -Br	α -OH	b 3 582	56	59	23	2.1
<i>IXa</i>	β -Br	β -OH ^b	b 3 583 b 3 557	50 76	28 31	25 23	1.1 1.1
<i>Xa</i>	α -Br	β -OH	b 3 586	47	58	25	2.3
—	β -Br	α -OH					
	5 α cholestan		f 3 622	—	85	16	2.1

^a In tetrachloromethane; f free, b bonded, sh shoulder, $\Delta\nu = \nu_f - \nu_b$ for diols, $\Delta\nu = \nu_{(\text{alcohol})} - \nu_{(\text{bromohydrin})}$ for bromohydrins; $B = \pi/2 \cdot \epsilon^{(a)}$. $\Delta\nu_{1/2}^{(a)}$, ^b after graphical separation.

EXPERIMENTAL

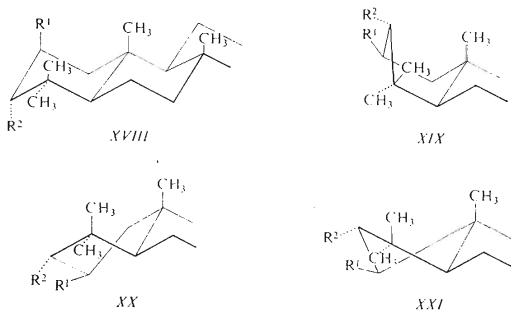
The infrared spectra were measured on a double beam grating spectrophotometer Unicam SP 700 calibrated with atmospheric water vapour. The spectral slit-width was within 3–5 cm⁻¹ interval. The band frequencies were determined with a ± 2 cm⁻¹ accuracy. The measurement was carried out at 25°C in infrasil cells of 2 or 4 cm width in tetrachloromethane. The concentrations were chosen so as to prevent the formation of intramolecular hydrogen bonds: for mono-hydroxy derivatives they were 4–10 · 10⁻³, for bromohydrins 2–5 · 10⁻³, and for diols 2–3 · 10⁻³ mol l⁻¹. All hydroxy derivatives were recrystallized from cyclohexane or n-hexane before measurement. The separation of the bands was carried out graphically, only in cases when both bands were distinctly resolved. The results are given in Table I.

The PMR spectra were measured at 100 MHz on a Varian HA-100 instrument with tetramethylsilane as internal reference, at 30°C. Deuteriochloroform was employed as solvent; if the

substances were poorly soluble, if the signals were superimposed with those of the $C_{(28)}H_2$ group, or in order to facilitate the analysis of the spectra, some spectra were measured in benzene, in mixtures of deuteriochloroform and hexadeuteriobenzene, or in pentadeuteriopyridine (Table II). The concentration of the solutions was between 0.1 and 0.3 mol l^{-1} . The multiplets of the protons in the positions 1, 2 and 3 were expanded to sweep width 50 or 100 Hz. For the identification of these signals double resonance experiments were made use of.

RESULTS AND DISCUSSION

Infrared spectra. Bromohydrins and diols of 2 β ,3 α -configuration when in chair form *XVIII* have both substituents in axial arrangement and hence they cannot form an intramolecular hydrogen bond. In the boat form (*XIX*, *XX*, *XXI*) the formation of the hydrogen bond is possible, so that the presence of a band of bonded hydroxyl may be considered a proof of the boat form². As is evident from Table I, in bromohydrins *VIIa*, *VIIIa* and in diol *Va* the boat form is valid; the shifts of the bonded hydroxyl bands ($\Delta\nu$) are comparable with the values found for diequatorial or axial-equatorial steroid derivatives^{14,15}. While in the spectrum of 2 β -bromo-3 α -hydroxy derivative *VIIIa* the band of the free hydroxyl group is not evident, meaning that the content of the chair form of *XVIII* must be negligible (see also^{5,6}), the 2 β -hydroxy-3 α -bromo derivative *VIIa* displays a weak band of a free hydroxyl group. This band can correspond to the chair form *XVIII*, or it may be caused by such a rotamer of the C—OH bond, where the O—H bond is oriented in the direction away from the bromine atom. Boul and coworkers¹⁶ found that even in diequatorial steroid halohydrins the formation of the intramolecular hydrogen bond is not complete and a part of the molecules exists in solution with a free hydroxy group; their content is very low. however. In our case we have not observed the band of a free hydroxyl either



in the diequatorial bromohydrin *Xa* (in chair form) or in bromohydrin *VIIIa* (in boat form). Therefore we suppose that the formation of the hydrogen bond – if allowed by the geometry of the ring A – is complete, and hence we assign the band of the free hydroxyl to the chair form of bromohydrin *VIIa* only, and the band of the bonded hydroxyl to the boat form. For the determination of the content of the boat form we used the ratio of apparent integrated intensities B_f/B_b under the supposition that the value B of the bonded hydroxyl in “pure” boat form and of the free hydroxyl in “pure” chair form are equal. This assumption can be supported by the results given in Table I: B -values of the bonded hydroxyl (bromohydrins *Xa* and *VIIIa*) and of the free hydroxyl (2 β -bromo-5 α -cholestan-3 α -ol) are practically identical and they move in the 2100–2300 range; the sum of the intensities in derivatives *VIIa* and *IXa* which contain two bands do not differ too much from this value. The population of the boat form of ring A in 2 β -hydroxy-3 α -bromo derivative *VIIa* determined by this method (85% in CCl_4) is in good agreement with the mean value obtained from the PMR spectra (88% in CDCl_3 , see Table III). The determination of the content of both forms in 2 β -bromo-3 β -hydroxy derivative *IXa* was also based on similar premises. This *cis*-bromohydrin can form a hydrogen bond both in the chair and boat form. In its spectrum two bands of bonded hydroxyl are present which differ by 26 cm^{-1} . We assign the band of lower frequency to the chair form (according to the value $\Delta\nu = 76\text{ cm}^{-1}$ it corresponds to the analogous derivative of 4,4-dimethyl-5 α -cholestane *IXc*, see⁶), and the second band ($\Delta\nu = 50\text{ cm}^{-1}$) to the boat form. The population of the boat form estimated from the B values (50%) is again in good agreement with the PMR data (Table III).

In diols *Va* and *VIa* the frequencies of the free and the bonded hydroxyl agree with the data published for analogous derivatives of 12-oleanene⁹ and lupane¹⁰. The shape of the doublet of 2 α ,3 β -diol *VIa* corresponds to a diequatorial diol ($\epsilon_f < \epsilon_b$, the narrow band of bonded hydroxyl) that of 2 β ,3 α -diol *Va* rather to an axial-equatorial diol ($\epsilon_f \approx \epsilon_b$, the broad band of bonded hydroxyl, see^{15,17}). Absorption intensity B of the free hydroxyl is approximately the same as in unsubstituted alcohols *Ia*–*IVa* but the intensity of the bonded hydroxyl is approximately double. In view of the presence of a free hydroxyl it is impossible to use the same procedure as for bromohydrins. However, as B_b -values for both diols *Va* and *VIa* are the same, as are B_f -values, we judge that in 2 β ,3 α -diol *Va* the boat form largely prevails. The presence of a larger amount of the chair form *XVIII* would manifest itself by an increase in B_f and decrease in B_b .

PMR spectra. In 2,3-disubstituted triterpenes four hydrogen atoms are present in ring A, that form an isolated system separated from the rest of the skeleton by quaternary carbon atoms $\text{C}_{(4)}$ and $\text{C}_{(10)}$. For conformational studies of similar derivatives only the coupling constant of the protons in positions 2 and 3 ($J_{2,3}$) has been used in earlier papers^{6–8,10}. This constant may be obtained directly from the spectra

by first order analysis if the signals of both protons are sufficiently separated. As the coupling constants of protons in positions 1 and 2 ($J_{1\alpha,2}$ and $J_{1\beta,2}$), or their sum ($\sum J_{1,2}$), may also be useful for the determination of the ring A conformation, we attempted a full analysis of this four-spin system.

In derivatives with polar substituents (Br, OH, OCOCH₃) in the positions 2 and 3 the signals of protons C₍₂₎-H and C₍₃₎-H appear at about 4 p.p.m. and they are sufficiently shifted from the signals of protons on C₍₁₎, which appear in the region about 2 p.p.m. (Table II). Therefore in the 100 MHz spectrum the mentioned system may be considered as an ABXY system. The protons in ring A are indicated as C₍₁₀₎-C₍₁₎H_AH_B-C₍₂₎R¹H_X-C₍₃₎R²H_Y-C₍₄₎, where R¹ and R² are Br, OH or OCOCH₃. As demonstrated by Abraham and Bernstein¹⁸ the ABXY system is not generally soluble in a manner which would afford explicit expressions for the frequencies and the intensities of the lines. Such expressions have been derived by Riggs¹⁹ for the case when ($J_{AX} - J_{BX} + J_{AY} - J_{BY}$) is negligibly small. In addition to this it may be demonstrated that the relations for a total of 16 lines (indicated by letters a, d, e, h in Riggs' paper¹⁹) are generally valid for the ABXY system even then when the above mentioned condition is not fulfilled. For the analysis of the spectra of 2,3-disubstituted derivatives we introduced the supposition that all vicinal coupling constants have the same sign (positive²⁰) and that the long-range coupling constants between the protons in the positions 1 and 3 are negligibly small ($J_{AY} \cong J_{BY} \cong 0$). The second supposition is justified because in none of the spectra we could observe a splitting or broadening of the lines in the AB-part or Y-part where the long-range coupling would be most evident; therefore the value of these coupling constants must be close to zero. In view of this supposition the Riggs' condition is reduced to $J_{AX} \cong J_{BX}$. In dependence on the validity of this condition and on the form of the AB and XY part and the separation of X and Y lines, or A and B lines, we analysed the spectra of single derivatives using one of the three following methods (in Table II they are indicated by 1, 2, 3): 1) Using the expressions derived by Riggs for the ABXY system¹⁹. 2) In the approximation ABPX according to Lee and Sutcliffe²¹ (where part PX corresponds to the protons indicated as X and Y) and subsequent application of relations which are generally valid for ABXY system to the outer lines of subquartets of the X part (lines a, d, e, h, see¹⁹). 3) As ABPX system²¹ where the part AB corresponds to the protons X and Y. By these procedures we obtained the values of the chemical shift, J_{XY} , sums $J_{AX} + J_{BX}$ and in some instances even the values of individual constants J_{AX} and J_{BX} ; the results are presented in Table II. It should be mentioned that the sum $J_{AX} + J_{BX}$ ($\sum J_{1,2}$) was in all cases; obtained from the separation of "general" lines (a, d, e, h according to¹⁹), under the sole supposition, i.e. that $J_{AY} + J_{BY} = 0$. Even if we admit that $|J_{AY} + J_{BY}|$ attains a value up to 2 Hz — which should manifest itself appreciably in the part Y —, the errors in the $\sum J_{1,2}$ value caused by this omission would in no case exceed the experimental errors given in Table II.

In 2 α ,3 β -derivatives *XVa* and *XVIa* the coupling constants $J_{2,3}$, $J_{1\alpha,2}$ and $J_{1\beta,2}$ are in agreement with the chair conformation of the ring A having both substituents in equatorial positions. In contrast to this in all 2 β ,3 α -derivatives (*Va*, *VIIa*, *VIIIa*, *XIa*–*XIVa*) both $J_{2,3}$ and $\sum J_{1,2}$ are much higher than would be expected for the chair form, which points to a distinct representation of the boat form. The same is true of 2 β -bromo-3 β -hydroxy derivative *IXa*; here we cannot base our conclusions on the $J_{2,3}$ value (it is in both forms approximately equal), but the high value of $\sum J_{1,2}$ clearly indicates the equilibrium of both forms. For the calculation of the population of the boat form in equilibria we made use of the values $J_{2,3}$ and $\sum J_{1,2}$; this was

made by a known method based on the averaging of the coupling constants observed during a sufficiently rapid interconversion of two conformers^{20,22}. However, the choice of suitable starting values for $J_{2,3}$ and $\sum J_{1,2}$ for the chair or the boat form of the ring A was a problem. The magnitude of the vicinal coupling constants depends not only on the dihedral angle of the C—H bonds, but also on the electronegativity of the substituents (which changes in the series of compounds investigated) and on the orientation of the C—H bonds with respect to these substituents^{23,24}. In addition to this, due to the interactions with the methyl groups a deformation of the chair form XVIII can take place with the change of the substituent in the position 2β and thus can change dihedral angles. In the boat form an additional factor enters into play: two classical boat forms of XIX and XX are possible (with $C_{(3)}$ and $C_{(10)}$ or $C_{(2)}$ and $C_{(5)}$ in stem-stern positions), to which corresponds one twist-form XXI. In view of the interactions between the polar substituents, methyl groups, and the hydrogen atoms on the ring B, it is difficult to estimate whether the energy minimum corresponds to the centre of pseudorotation between the forms XIX and XX or whether it lies closer to one of them. This uncertainty in geometry does not affect $J_{2,3}$ too much (where, according to models, during the pseudorotation between the forms XIX and XX the dihedral angle does not change too much), but it affects rather $J_{1\alpha,2}$ and $J_{1\beta,2}$ where the dihedral angles differ substantially. Unfortunately the endeavour to acquire information on the true geometry of the boat form in 2β -bromo derivatives VIIIa, VIIIb and XIIIa was unsuccessful because it was not possible to obtain the values for $J_{1\alpha,2}$ and $J_{1\beta,2}$, due to the degeneration of the AB part of the spectra.

Although a series of papers exists which study in detail the influence of the above mentioned effects on the magnitude of the vicinal coupling constants (for a review see²⁴) in sets of model substances, the application of the observed approximate quantitative relationships on a different structural type is always problematic. This is especially true if — as in our case — it is complicated by the uncertainties in the geometry of the compounds studied. In order to obtain as convincing a picture as possible of the equilibrium population of the boat form in the ring A, to evaluate the significance of the contributions of single effect, and to obtain a method also applicable for further conformational studies of triterpenes, we employed four various methods (A, B, C, D) for the calculation of the boat population differing both by the measure of the neglect of the effect of substituents on J , and by the choice of the structural model. All four methods make use of a cyclic structural model; preliminary calculations based on the described relations $J = f(\Phi)$, derived from acyclic models^{25,26}, afforded evidently unrealistic values for the starting J , and thus also for the population of the boat form.

Method A: The structural model is cyclohexane and the effect of substituents is completely neglected. As $J_{1,2}$ and $J_{2,3}$ values in the chair form of the ring A and $J_{2,3}$ value in the boat form the experimentally found²⁷ coupling constants in octadecate-

riocyclohexane are used (at -103°C when the rate of interconversion is sufficiently slow $J_{a,a} = 13.12$ Hz, $J_{a,e} = 3.65$ Hz, $J_{e,e} = 2.96$ Hz). According to lit.²⁷ these values correspond to dihedral angles $\Phi = 175^{\circ}$, 57° , or 61° when the angle between the geminal hydrogen atoms is $\omega = 118^{\circ}$ (the H—C—H angle in Newman projection) and they lead to the values of coefficients $A = 12.95$ and $n = -0.02$ in the general relation $J = A(\cos^2 \Phi + n \cdot \cos \Phi)$. This relation was used to obtain $J_{1,2}$ in boat forms. In view of the above indicated angles we chose for the classical boat forms XIX and XX $\Phi_{1\alpha,2\alpha} = 0^{\circ}$ or 57° , respectively, and $\Phi_{1\beta,2\alpha} = 118^{\circ}$ or 61° , respectively, and for the twist-form XXI their mean values (28.5° and 89.5°). The possible differences in valence angles and the changes in the dihedral H—C₍₂₎—C₍₃₎—H angle in the pseudorotation of the boat form are neglected.

Method B makes use of the same model and the relation $J = f(\Phi)$ as the method A, but it comprizes the effect of the electronegativity of the substituents, without, however, taking into consideration the effect of their orientation with respect to the coupled hydrogens. Characteristic values $J_{1,2}$ and $J_{2,3}$ are corrected using the well known additive relation²⁸ $J_{\text{kor.}} = J(1 + k \sum \Delta E_{X_i})$ in which J means the vicinal coupling constant in the unsubstituted fragment (cyclohexane), ΔE_{X_i} is the difference in the electronegativity of the first atom of the substituent and the hydrogen atom, and k is the coefficient depending on the type of compound. In our case we used Pauling's electronegativity²⁹ and for k we chose the value -0.05 which of a series of tested values gave the best results (*i.e.* a minimum number of the values of population of the boat form, higher than 100%, and the best mutual agreement of the results from $J_{2,3}$ and $\sum J_{1,2}$).

Method C: The model used and the general term for the correction of J for the electronegativity of substituents are the same as in the method B; in addition to this the effect of the orientation of the substituent with respect to the coupled hydrogens is also taken in consideration (the coefficient k is the function of the dihedral angle X—C—C—H). The corresponding values k are taken from the empirically obtained graphical dependence on the dihedral angle, described by Bystrov²⁴.

Method D: As starting values of $J_{2,3}$ and $\sum J_{1,2}$ for the chair and the boat forms the values are used which were found in selected steroid and triterpenoid derivatives in which one of the two forms distinctly predominates. For the chair form we chose $J_{2,3} = 3$ Hz and $\sum J_{1,2} = 7$ Hz as the mean values, obtained from a series of 2 β -substituted derivatives of 4,4-dimethyl-5 α -cholestane^{6,7}, 4,4-dimethyl-5 α -estrane³⁰, lupane¹⁰, 18 α -oleanane³¹ and 24-nor-18 α -oleanane³², which seem to be the closest analogies. For the boat form we used $J_{2,3} = 12$ Hz and $\sum J_{1,2} = 18.2$ Hz, obtained as an average of the values found in 2 β -bromo-3 α -hydroxy derivatives VIIIa and VIIIb and in 2 β -bromo-3 α -acetoxy derivative XIIIa (in CDCl₃, see Table II). For bromohydrin VIIIa it was found independently by infrared spectroscopy that in non-polar solvents it exists practically only in the boat form. The mentioned starting

values were used for a whole set of derivatives and, hence, we neglected the differences in the electronegativities of substituents. On the other hand this method eliminates the errors caused by the choice of the dihedral angles.

For a comparison with the behaviour of 2,3-disubstituted derivatives it was interesting to determine the effect of the presence of the 2 β -substituent alone (OH, OCOCH₃) on the conformation of ring A. The observed values of the sum of four vicinal coupling constants ($\sum J_{1,2} + \sum J_{2,3}$) in 2 β -hydroxy derivative *Ia* and 2 β -acetoxy derivative *XVIIa* are too high for the chair form and they must correspond to the equilibrium of both forms. The calculation of the population of the boat form was carried out in the same manner as in the case of disubstituted derivatives (but from $\sum J_{1,2} + \sum J_{2,3}$) by methods *A*, *B*, *C* and *D*. For the method *D* we used as the starting value of $\sum J_{1,2} + \sum J_{2,3}$ for the chair form 14 Hz, and for the boat form 36 Hz, on the basis of the above mentioned $\sum J_{1,2}$ and $\sum J_{2,3}$ values in 1,2-disubstituted derivatives³¹.

The populations of the boat form of the ring A, calculated by the methods *A*, *B*, *C* and *D*, are summarized in Table III. As in contrast to $J_{2,3}$ the $\sum J_{1,2}$ value is strongly dependent on the geometry of the boat form, the values of the populations calculated from $\sum J_{1,2}$ are also very sensitive to its geometry. The testing calculations by methods *A*, *B* and *C* for classical boat forms *XIX* and *XX* exclude practically the existence of the ring A in these forms because they give unreasonably high values (much higher than 100%; these results are not given in Table III). This leads to an unambiguous conclusion regarding the preference of the twist-form of *XXI* which affords values (given in Table III) that are in good agreement with the results obtained from $J_{2,3}$. A more accurate determination of the geometry of this form (*i.e.* the deviations of the angle of pseudorotation in the direction to *XIX* or *XX*) from $\sum J_{1,2}$ would not be convincing in view of the approximate character of the methods *A*, *B* and *C*. The comparison of the calculated values for populations, obtained from $J_{2,3}$ and $\sum J_{1,2}$ by all methods, indicates a relatively good agreement. As we do not have clear-cut reasons for the preference of the results obtained by one of the methods used (method *C* should in fact describe the effect of substituents most completely, but the accuracy of the corrections and the choice of the dihedral angles, especially in the boat form, is problematic), we give in Table III the "mean values" of the populations (average of all values calculated), which should — according to our opinion with an at least $\pm 10\%$ precision — reliably describe the equilibrium proportion of the boat and the chair form of the ring A. A certain criterion of accuracy is the already mentioned agreement with the results obtained from infrared spectra. For the sake of comparison the estimations of maximum and minimum values of the population of the boat form in derivatives of 4,4-dimethyl-5 α -cholestane (*c*) and 8-lanostene (*d*) are also comprized in Table III, which were obtained by method *D* from first-order coupling constants published by Levisalles and coworkers⁶⁻⁸.

From the data given in Table III and from the results of the infrared spectra the

TABLE II
Coupling Constants and Chemical Shifts of Protons in Ring A^a

Com- pound	Substituents in position		Solvent	$J_{2,3}$	$\sum J_{1,2}$	$J_{1\alpha,2}$	$J_{1\beta,2}$	$-J_{1\alpha,1\beta}$	$\delta 3\text{H}$	$\delta 2\text{H}$	$\delta 1\alpha\text{H}$	$\delta 1\beta\text{H}$	Way of analysis ^b
	2	3											
Va	$\beta\text{-OH}$	$\alpha\text{-OH}$	$\text{C}_5\text{D}_5\text{N}^c$	8.4	14.3	~ 7.1	~ 7.1	13.2	3.84	4.08	(1.90)	(1.73)	1
XIa	$\beta\text{-OAc}$	$\alpha\text{-OAc}$	CDCl_3	8.0	13.6	d	d	d	5.10	4.98	~ 1.68	~ 1.68	1
VIIa	$\beta\text{-OH}$	$\alpha\text{-Br}$	CDCl_3	11.2	16.2	(8.3)	(7.9)	13.8	4.52	3.97	(1.95)	(1.58)	1
			$\text{C}_5\text{D}_5\text{N}^c$	7.1	11.7	d	d	d	4.61	4.37	~ 1.89	~ 1.89	1
XIIa	$\beta\text{-OAc}$	$\alpha\text{-Br}$	CDCl_3	8.1	12.3	(6.8)	(5.5)	~ 14	4.36	5.25	(1.93)	(1.67)	2
VIIIa	$\beta\text{-Br}$	$\alpha\text{-OH}$	CDCl_3	11.9	18.3	d	d	d	3.88	4.34	~ 2.14	~ 2.14	1
			$\text{C}_5\text{D}_5\text{N}^c$	11.9	17.4	d	d	d	4.03	4.51	~ 2.14	~ 2.14	1
VIIIb	$\beta\text{-Br}$	$\alpha\text{-OH}$	CDCl_3	12.1	18.0	d	d	d	3.88	4.34	~ 2.15	~ 2.15	1
XIIIa	$\beta\text{-Br}$	$\alpha\text{-OAc}$	CDCl_3	12.0	18.4	d	d	d	5.37	4.28	~ 2.15	~ 2.15	1
XIVa	$\beta\text{-Br}$	$\alpha\text{-Br}$	C_6H_6	9.6	14.7	~ 7	~ 7	14.6	4.64	4.53	(2.23)	(2.12)	1
IXa	$\beta\text{-Br}$	$\beta\text{-OH}$	CDCl_3	3.2	13.3	(6.9)	(6.4)	14.7	~ 3.41	4.67	(2.30)	(1.81)	2
			$\text{CDCl}_3 +$ $+ \text{C}_6\text{D}_6$ 1:1	3.2	13.6	(7.2)	(6.4)	14.5	~ 3.22	4.44	(2.20)	(<1.60)	2
XVa	$\alpha\text{-OAc}$	$\beta\text{-OAc}$	CDCl_3	10.4	16.4	≥ 11.7	≤ 4.7	d	4.74	5.12	d	d	3
XVIa	$\alpha\text{-Br}$	$\beta\text{-Br}$	CDCl_3	11.3	16.7	12.2	4.5	13.1	4.00	4.49	~ 1.58	2.57	3
Ia	$\beta\text{-OH}$	--	CDCl_3	d	$26.0^{e,f}$	d	d	d	d	4.05	d	d	e
XVIIa	$\beta\text{-OAc}$	--	CDCl_3	d	21.9^e	d	d	d	d	5.08	d	d	e

^a Chemical shifts in p.p.m. (δ -scale) rounded up to 0.01 p.p.m., accuracy ± 0.005 p.p.m. Coupling constants in Hz, accuracy for $J_{2,3}$, $\sum J_{1,2}$ and $J_{1\alpha,1\beta} \pm 0.2$ Hz, for $J_{1\alpha,2}$ and $J_{1\beta,2} \pm 0.3$ Hz. The values given in parentheses are assigned tentatively and may be mutually interchanged; ^b for the significance of the symbols 1, 2 and 3 see the text; ^c with a trace of CD_3COOD ; ^d undeterminable values; ^e sum of four coupling constants ($\sum J_{1,2} + \sum J_{2,3}$) obtained as the separation of the outer lines of the multiplet ($\text{C}_{2,3}$)-H; ^f after addition of CF_3COOD 27.6 Hz.

TABLE III

Populations for the Boat Form of the Ring A (in %) in β -Substituted Derivatives of 19 β ,28-Epoxy-18 α -oleanane (a), 4,4-Dimethyl-5 α -cholestan-3 α and 8-Lanostene (d)

Derivative	Substituents in position	Solvent	Series a												Mean value ^b	Series c	Series c
			from J _{2,3} by the method						from $\sum J_{1,2}$ by the method ^e								
			A	B	C	D	A	B	C	D							
V	β -OH α -OH	C ₅ D ₅ N	54	67	62	60	62	71	74	65	64	—	—				
XI	β -OAc α -OAc	CDCl ₃	50	62	56	56	56	65	70	59	59	—	—				
VII	β -OH α -Br	CDCl ₃	81	94	93	91	77	87	97	82	88	~ 50	~ 60				
		C ₅ D ₅ N	41	49	43	46	41	48	58	42	46	—	—				
XII	β -OAc α -Br	CDCl ₃	51	60	55	57	46	53	63	47	54	< 20	< 30				
VIII	β -Br α -OH	CDCl ₃	88	102	102	99	94	100	104	101	99	~ 100	—				
		C ₅ D ₅ N	88	102	102	99	87	92	97	93	95	—	—				
XIII	β -Br α -OAc	CDCl ₃	89	103	103	100	95	101	105	102	100	> 70	—				
XIV	β -Br α -Br	C ₆ H ₆	65	73	71	73	65	70	74	69	70	< 20	—				
IX	β -Br β -OH	CDCl ₃	d	d	d	d	54	58	62	56	58	< 40	—				
		CDCl ₃ + C ₆ H ₆ 1:1	d	d	d	d	56	60	65	59	60	—	—				
I ^e	β -OH —	CDCl ₃	—	—	—	—	56	65	70	54	61	< 30	< 30				
XVII ^e	β -OAc —	CDCl ₃	—	—	—	—	39	46	51	35	43	< 20	< 20				

^a The results for the twist-boat *XXI*; ^b arithmetical mean of all values given; ^c taken or estimated from the literature data⁶⁻⁸; ^d cannot be determined because $J_{2,3}$ is in both forms practically the same; ^e for the calculation $\sum J_{1,2} + \sum J_{2,3}$ was used.

following conclusions follow for the conformation of the ring A in triterpene derivatives of the series *a*: In derivatives which contain only an oxygen function in the position 2 β (*Ia*, *XVIIa*) the interactions between the 2 β -substituent and 4 β - and 10 β -methyl groups increase the energy of the chair form *XVIII* ($R^1 = \text{OH}, \text{OCOCH}_3$; $R^2 = \text{H}$) to such an extent that the chair and the boat form appear in equilibrium in comparable amounts. The introduction of a further substituent into the position 3 α ($R^2 = \text{Br}, \text{OH}, \text{OCOCH}_3$) does not substantially affect the position of the equilibrium in such cases when formation of an intramolecular hydrogen bond is impossible, *i.e.* in hydroxy derivatives *Va* and *VIIa* in pyridine, and in acetates *XIa* and *XIIa*. The content of the boat form in all these derivatives is about 50%; small differences between single substituents, as well as the effect of the polarity of the solvent on equilibrium cannot be discussed, due to the errors committed during the determination of the position of the equilibrium. Hence, it seems that the presence and the nature of the 3 α -substituent (R^2) does not have an important effect, which means that the interactions of the axial substituent R^2 in the chair form *XVIII* are compensated in the boat form both by the interactions between the substituents R^1 and R^2 , and by the interactions between R^2 and the methyl groups on $C_{(4)}$. The presence of the intramolecular hydrogen bond in derivatives *Va* and *VIIa* in non-polar solvents manifests itself by an equilibrium shift towards the boat form. From the comparison of the data for 2 β -hydroxy-3 α -bromo derivative *VIIa* in non-polar solvents and in pyridine it follows that the stabilization of the boat form, caused by the hydrogen bond, is about 1 kcal mol⁻¹. In diol *Va* this energy cannot be estimated in consequence of the inaccuracy of the data, but the results are not in contradiction with an approximately equal value. If bromine is bound in the position 2 β the chair form *XVIII* ($R^1 = \text{Br}, R^2 = \text{OH}, \text{OCOCH}_3$) is much less stable than the boat form; the equilibrium is shifted practically completely to the side of the boat form even when this form is not stabilized by a hydrogen bond. Dibromo derivative *XIVa* is an exception; in it about 30% of the chair form *XVIII* is present ($R^1 = R^2 = \text{Br}$); evidently the interaction between the dipoles of the C—Br bonds is operative in this case, which destabilizes the boat form. The same effect was observed⁷ in steroid dibromo derivative *XIVc*. From the comparison of *trans*-bromohydrin *VIIIa* and *cis*-bromohydrin *IXa* it is evident that the change of configuration of the hydroxyl group in the position 3 has a shift of the equilibrium in the direction of the chair form as a consequence. The same phenomenon may be observed in diols and diacetate derivatives: 2 β ,3 α -diol *Va* and diacetate *XIa* contain about 60% of the boat form, while the isomeric 2 β ,3 β -diol and its diacetate, derived from lupane, have according to ref.¹⁰ the ring A practically exclusively in the chair form. This effect may be explained by the fact that in contrast to 2 β ,3 α -derivatives, the boat form in the 2 β ,3 β -isomers is destabilized by the interaction between the 10 β -methyl and 3 β -hydroxyl group, which are in flagpole positions when the geometry of the boat form is closer to the form *XIX*.

In triterpenic derivatives of the series *a* the presence of bromine in the position 2 β manifests itself by a far higher proportion of the boat form than the presence of the oxygen function in this position; the same is true of derivatives of 4,4-dimethyl-5 α -cholestane (*c*)^{6,7}. This effect may be observed on comparison of 2 β ,3 α -derivatives *VIII* and *V*, *XIII* and *XI*, which differ only by the 2 β -substituent R^1 , and also on comparison of derivatives *VIII* and *VII*, *XIII* and *XII*, where the groups R^1 and R^2 are interchanged. It also appears in *cis*-derivatives on comparison of 2 β -bromo-3 β -hydroxy derivative *IXa* (~60% of the boat form) with 2 β ,3 β -lupanediol which according to lit.¹⁰ exists in the chair form only. The difference between the effect of bromine and the oxygen function on the position of the chair-boat equilibrium, expressed as a difference in ΔG^0 values, is in all above compared cases higher than 1 kcal mol⁻¹. This value should be considered as minimum, because in cases when the equilibrium is shifted far to the side of one form, the value 90% was used for its content during the calculation. If the steric and polar interactions in the boat and chair forms of the ring A are also taken into consideration as well as the fact that this effect becomes evident during the comparison of differently substituted derivatives of 2 β ,3 α and 2 β ,3 β -configuration, it may be excluded that they are caused by other factors (for example by interactions of the substituents R^2) than 1,3-*syn*-axial interactions between the 2 β -substituent (R^1) and both methyl groups in the chair form *XVIII*.* From this the conclusion can be drawn that 1,3-*syn*-axial interaction CH₃/Br is at least 0.5 kcal mol⁻¹ larger than the interaction CH₃/OH or CH₃/OCOCH₃. The published values obtained from simple derivatives of cyclohexane and decalin show, however, rather the opposite trend (CH₃/Br 2.2 kcal mol⁻¹, see³⁵; CH₃/OH 2.2–2.7 kcal mol⁻¹, see^{36–38}). This contradiction is probably caused by the fact that the value for the interaction CH₃/Br was obtained³⁵ from derivatives of 2-bromocyclohexanone where the distances between the interacting groups can be substantially different from the distances in the decalin type derivatives which do not contain a carbonyl group either. According to our results it may be expected that the energy of 1,3-*syn*-axial interaction of CH₃/Br is about 3 kcal mol⁻¹, or higher (however, the value 15 kcal mol⁻¹ obtained by theoretical calculation³⁹ seems excessive).

From Table III it is further evident that between triterpenic derivatives of the series *a* and 4,4-dimethylsteroid derivatives of the series *c* and *d* substantial differences exist in the positions of the chair-boat equilibrium. As was already shown

* In the boat form the interaction between the 2 β -substituent and the 1 β -hydrogen is also operative; this interaction, if the geometry is close to the form *XIX*, could attain a maximum value of the eclipsing interaction. However, in our case this does not play a role because according to the heights of the barriers of internal rotation in ethanol³³ and ethyl bromide³⁴ the eclipsing interaction of Br/H is larger than that of OH/H which leads to a higher destabilization of the boat form in bromo derivatives than in hydroxy derivatives. Hence the lower limit, further considered for the difference of 1,3-*syn*-axial interactions in the chair form *XVIII* (0.5 kcal mol⁻¹), would be shifted still higher.

by Lacoume and Levisalles⁸ the derivatives of the series *c* and *d* behave in an analogous manner, so that the presence of the 8(9)-double bond does not have any important effect. In triterpenes the equilibrium is shifted in all cases more to the side of the boat form which agrees with the results derived from the stereochemistry of the opening of 2 β ,3 β -epoxides and from the isomerization equilibria of 2-bromo-3-oxo derivatives^{4,11}. In the case of these reactions it was found¹¹ that the difference between the derivatives of the series *a* and *b*, and the series *c* and *d* is 0.5–0.7 kcal mol⁻¹ in favour of the boat form in triterpenes. In view of the low accuracy of the determination of the positions of conformational equilibria it is impossible to evaluate accurately the difference in the values ΔG° of the chair–boat equilibrium for derivatives listed in Table III, but it is possible to estimate that it must be higher than 0.5 kcal mol⁻¹ and that it is about 1 kcal mol⁻¹. Although the derivatives of the series *a*, *b*, *c*, *d* differ, beginning with the ring D, we believe that the differences in the skeletons do not play an important role and this effect is caused by the 8 β -methyl group. The repulsions between the axial methyl groups on C₍₈₎ and C₍₁₀₎ lead to a deformation of the ring B; this is indicated by the dipole moments of various lupane derivatives⁴⁰ and by the X-ray diffraction of 8-methyltestosterone⁴¹. If the ring A is in the chair form XVIII the interactions between the axial methyl groups on C₍₄₎ and C₍₁₀₎, or also between the axial substituent on C₍₂₎ lead to a further deformation of the skeleton. From the diffraction data published for adiantol B bromoacetate⁴² (21 β H-hopan-22-ol bromoacetate), it may be inferred that the molecule of the triterpene is appreciably bent; for example the planes of the rings A, B and C (planes given by the carbon atoms 1, 2, 4, 5; 6, 7, 9, 10 or 8, 11, 12, 14) are not parallel. The planes of the rings A and B close an angle of about 15°, the planes of the rings A and C an angle of about 24°. The distances C₍₄₎–C₍₁₀₎ and C₍₈₎–C₍₁₀₎ are increased (~ 2.7 Å) and the maximum differences against the ideal geometry appear in the distances of the carbon atoms of the methyl groups 4 β ,10 β and 8 β ,10 β (3.20 or 3.13 Å resp.). In the boat form of the ring A 1,3-*syn*-axial interaction of the 4 β and 10 β -methyl groups and the 2 β -substituent disappear; in addition to this the boat form is flexible so that the deformation of the ring B does not cause a further increase in energy (as in the chair form). We consider, therefore, that the specific effect of the 8 β -methyl group consists in the fact that this group destabilizes the chair form more than the boat form of the ring A. This effect is quite general and is also observable in derivatives substituted in the positions 1 and 2 (see³¹).

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