CONFORMATION OF THE RING A IN 2,3-DISUBSTITUTED 24-NORTRITERPENES AND THE STEREOCHEMISTRY OF THE OPENING OF 2β,3β-EPOXIDES*

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Bromo ketones *VI*, *XVI* and *XIX* and bromohydrins *IX*, *X*, *XII* and *XV* were prepared from 19β,28-epoxy-24-nor-18α-oleanan-3-one (*III*) and their structure was confirmed by a series of reactions. The conformation of the ring A of these derivatives was deduced from the infrared, ultraviolet and ^{1}H—NMR spectra and from circular dichroism. In 2β-bromo-3-oxo-derivative *XIX* the chair and the boat forms occur at equilibrium in an approximately 1 : 1 ratio, while in 2β-bromo-3α-hydroxy-derivative *XV* the boat form is populated only negligibly (~7%). The opening of β-epoxide *VIII* with hydrobromic acid gives rise to 77% of the normal (diaxial) product *XII* and 23% of the anomalous (diequatorial) product *IX*. The effect of the methyl groups on the ring A conformation and the stereochemistry of the 2β,3β-epoxide opening, as well as the effect of bromine in the α-position on the stereochemistry of the reduction of ketones with sodium borohydride are discussed.

In past years the conformation of the ring A in various steroidal and triterpenoid derivatives of 5α-configuration, differing by substitution with the methyl groups on $C_{(4)}$, $C_{(8)}$ and $C_{(10)}$, was investigated in detail. The majority of the studies concerned 2,3-disubstituted derivatives (predominantly bromo ketones and bromohydrins) which have methyl groups in the positions 10β (5α-androstane[1], 5α-cholestane[2-4]), 4α and 4β (4,4-dimethyl-5α-estrane[5]), 4α,4β and 10β (4,4-dimethyl--5α-cholestane[6,7], lanostane[8], 8-lanostene[8,9]), and 4α,4β, 8β and 10β (19β,28-epoxy--18α-oleanane[3,10-12], 20β,28-epoxy-18α,19β*H*-ursane[11,12], 25,26,27-trinordammaran-24,20-olide[10]). From the comparison of the results published in the papers mentioned it is evident that in the derivatives with a 2β substituent the population of the boat form of ring A increases with the increasing number of the axial methyl groups on the β-side of the molecule. The same effect may also be observed in the stereochemistry of the 2β,3β-epoxide opening[5,8,13]. For the comparison of the effect of single methyl groups on the stereochemistry of the ring A we complete this series

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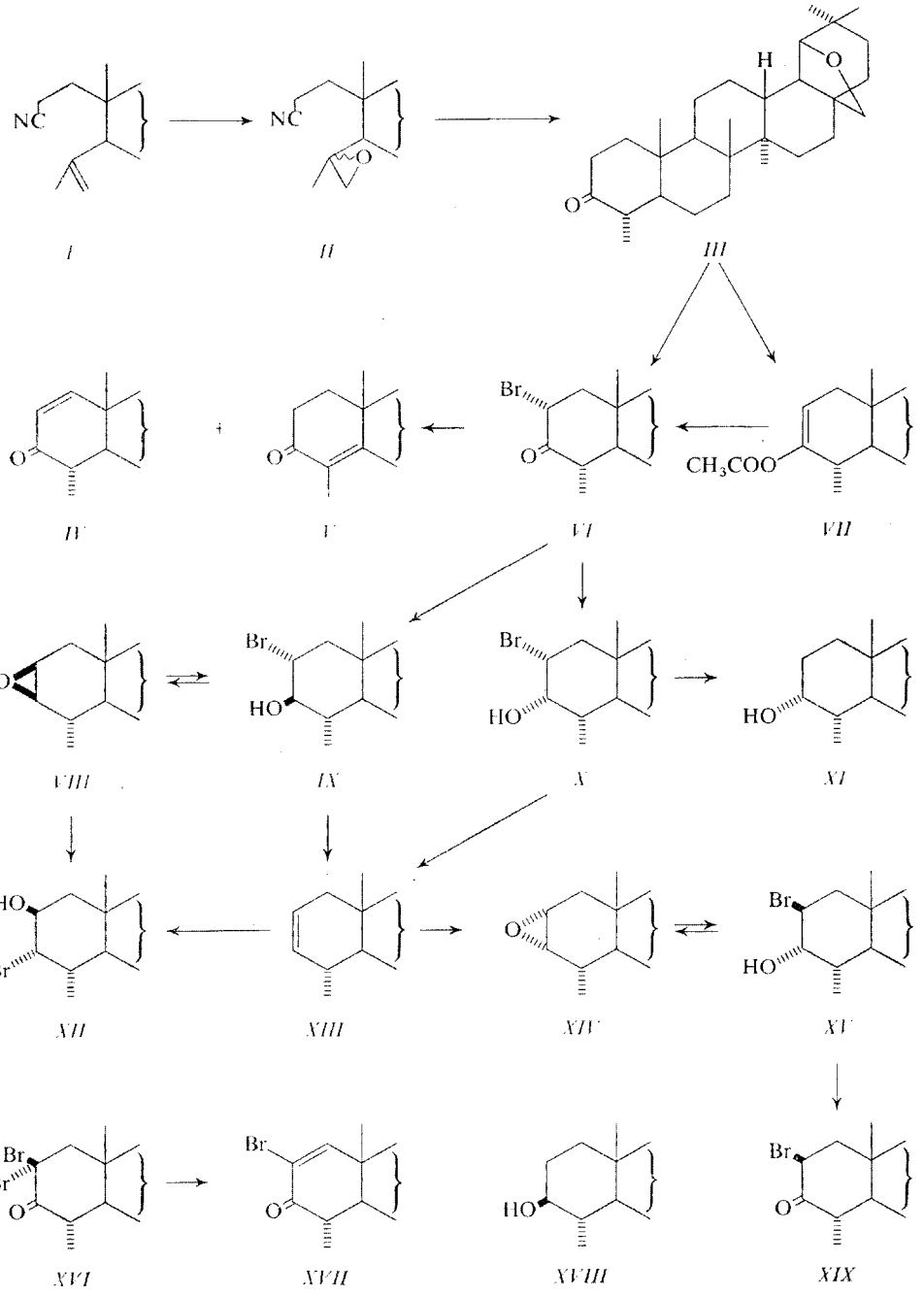
of compounds in this paper by 2,3-disubstituted derivatives of 24-nortriterpenes which contain the methyl groups in the position 4α,8β and 10β. The study was carried out with the derivatives of 19β,28-epoxy-24-nor-18α-oleanane, using ketone *III* obtained from the easily available 3,4-secodinitrile *I* as starting compound.

The conversion of nitrile *I* to ketone *III* by a five-step procedure, *via* epoxynitrile *II* or by direct acid catalysed cyclization of the analogous epoxy acid has already been described[14]; the yields of these procedures are very low, however. Application of a recently published[15] general method of preparation of 4α-methyl-3-oxo derivatives (direct cyclization of epoxynitriles under the effect of boron trifluoride etherate in boiling toluene) on epoxynitrile *II* gave ketone *III* in high yield (up to 90%). Reaction of ketone *III* with isopropenyl acetate under catalysis with *p*-toluenesulfonic acid gave an enol acetate to which the structure *VII* was assigned in analogy to[16,17]. In the experiments aiming at the preparation of the isomeric enol acetate with the double bond in the position 3(4) under the effect of acetic anhydride and perchloric acid in tetrachloromethane (ref.[17]) or by boiling in acetic anhydride in the presence of *p*-toluenesulfonic acid the opening of the ether bridge in the ring E already took place. Kinetically controlled bromination of enol acetate *VII* gave 2α-bromoketone *VI* similarly as in steroid derivatives[16,18]; the position of bromine follows from the presence of the 4α-methyl group doublet and the characteristic ABX system of protons in the position 1 and 2 in the ^{1}H-NMR spectrum (Table I). This also corroborated the presence of the 2(3)-double bond in enol acetate *VII*. Similarly as in steroidal 4α-methyl-3-oxo derivative[19] the kinetically controlled bromination of ketone *III* also led to 2α-bromo ketone *VI*; as a by-product 2,2-dibromo ketone *XVI* was isolated, the structure of which was confirmed by its ^{1}H-NMR spectrum (a doublet of the 4α-methyl group and two doublets of protons in the position 1). From dibromo ketone *XVI* an unsaturated bromo ketone was obtained under the effect of collidine or lithium chloride in dimethylformamide. The absorption in the infrared (1698, 1601 cm^{-1}) and the ultraviolet region (256 nm, log ε 3·83) of this bromoketone is in good agreement with the structure *XVII*. Dehydrobromination of dibromo ketone *XVI* to derivative *XVII* also takes place in acid medium.

Dehydrobromination of 2α-bromo ketone *VI* with collidine or lithium chloride in dimethylformamide gave unsaturated ketone *IV* as the main product. It was accompanied by a considerable amount of the rearranged product *V* (see[20]). It is interesting that the isomer *V* is formed from 2α-bromo ketone *VI* under the effect of hydrobromic acid; probably a rearrangement of bromine from $C_{(2)}$ to $C_{(4)}$ takes place first and then the 4-bromo ketone formed eliminates hydrogen bromide. A similar rearrangement of 2-bromo derivative to 4-bromo derivative in acid medium has also been observed in steroidal 2-methyl-2-oxo derivatives[21]. The assignment of the structures of α,β-unsaturated ketones *IV* and *V* was confirmed by comparison of their infrared and ultraviolet spectra: isomer *V* with the 4(5)-double bond gives a distinct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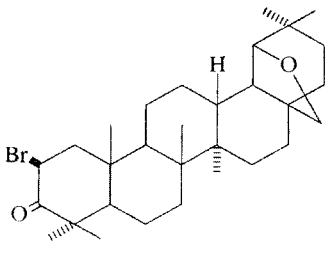
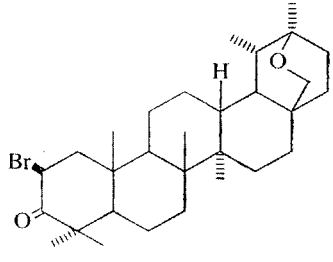
band of the C=C vibration (1613 cm^{-1}), a lower frequency of the C=O vibration (1663 cm^{-1}), a higher λ_{max} value and a higher intensity of the $\pi - \pi^*$ transition (243 nm, log ε 4·16) than the isomer *IV* with the 1(2)-double bond (the ν(C=C) band cannot be observed, see[16]; ν(C=O) 1678 cm^{-1}; λ_{max} 224 nm, log ε 3·96). The same relationships also follow from the comparison of the spectral data published for analogous steroidal 4-methyl-3-oxo derivatives[16,17]. The ^{1}H-NMR spectrum of isomer *V* confirms the presence of the methyl group on the double bond (singlet at 1·79 p.p.m.) and the absence of olefinic hydrogens.

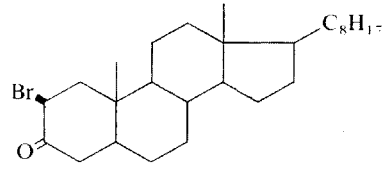
On reduction of 2α-bromo ketone *VI* with sodium borohydride a mixture of both isomeric bromohydrins *IX* and *X* was formed. Their structure follows from the reaction with potassium hydroxide: *trans*-bromohydrin *IX* afforded β-epoxide *VIII*, while the *cis*-bromohydrin *X* gave ketone *III* as the main product in addition to a small amount of an unidentified substance which according to its infrared spectrum contains an aldehyde group (evidently an aldehyde with a five-membered ring A; a similar ring contraction was also observed in the case of 1α-hydroxy-2α-bromo derivative[13] during the reaction with hydroxide). *cis*-Bromohydrin *X* was converted to 3α-hydroxy derivative *XI* under the effect of hydrogen on palladium catalyst. Compound *XI* was also obtained as a by-product on reduction of ketone *III* with sodium borohydride. The main product of this reaction was 3β-isomer *XVIII*, as expected[15,16]. The assignment of the configurations of alcohols *XI* and *XVIII* is based on the signal of hydrogen in the position 3 in the ^{1}H-NMR spectra (Table I). In the equatorial alcohol *XVIII* it appears at higher fields as a doublet of triplets and the



XX



XXI



XXII

sum of the three vicinal coupling constants is 25 Hz; in the axial alcohol *XI* it is at lower field and it forms a quartet (sum of coupling constants ~7·5 Hz). The comparison of the course of the reduction of ketones *III* and *VI* with sodium borohydride is also interesting. While in the case of unsubstituted ketone *III* the equatorial alcohol *XVIII* predominates over the axial alcohol *XI* (in a 9 : 2 ratio), in the reduction of 2α-bromo ketone *VI* bromohydrin *X* with the axial 3α-hydroxyl group prevails over the isomer *IX* in a 3 : 2 ratio (both ratios were estimated from the yields of the chromatographic separation of the isomers). Hence the presence of bromine in the α-position affects the stereochemistry of the reduction of the oxo group in favour of the *cis*-bromohydrin formation. A similar effect of bromine was also observed in the reduction of isomeric 2-bromo-1-oxo derivatives[13] and it also appears — though less distinctly — in 2α-bromo-3-oxosteroids, as follows from the comparison of data in the literature[22,23]. It seems, therefore, that this effect of bromine has a more general character, which is also confirmed by some examples from the steroid series[24].

Reaction of the crude mixture of bromohydrins *IX* and *X* with zinc in acetic acid gave olefin *XIII* which afforded α-epoxide *XIV* under the effect of 3-chloroperoxybenzoic acid. Attempts at the preparation of olefin *XIII* by dehydration of alcohol *XI* or *XVIII* with phosphorus oxychloride in pyridine or with thionyl chloride in benzene were not successful, because they gave unseparable mixtures of products. Lithium aluminium hydride reduction of *4*-toluenesulfonylhydrazone[25] prepared from ketone *III* also gave a mixture of the saturated derivative and olefin *XIII* which could be separated only with difficulty, and from which α-epoxide *XIV* was isolated after epoxidation in low yield. From α-epoxide *XIV* 2β-bromo-3α-hydroxy derivative *XV* was isolated after reaction with hydrobromic acid as the sole product. Its *trans* configuration was confirmed by its conversion to epoxide *XIV* with potassium hydroxide. Oxidation of bromohydrin *XV* with sodium dichromate in acetic acid and in the presence of sodium acetate[6] gave 2β-bromo ketone *XIX* which is very unstable and isomerizes rapidly to 2α-isomer *VI*. Reaction of β-epoxide *VIII* with hydrobromic acid did not give a single derivative as in the case of α-epoxide *XIV*, but two bromohydrins; one of them was identical with 2α-bromo-3β-hydroxy-derivative *IX*, obtained on reduction of bromo ketone *VI*, while the second was also prepared by reaction of olefin *XIII* with N-bromosuccinimide and dimethyl sulfoxide in the presence of water[26] and therefore it should be assigned the structure of 2β-hydroxy-3α-bromo derivative *XII*.

The spectral data of the derivatives prepared are summarized in Tables I—III. In 2α-bromo derivatives *VI*, *IX* and *X* these data correspond to the chair form of ring A, similarly as in analogous compounds in other steroid and triterpenoid series[1–12]. The differences in the conformation of ring A appear in derivatives which contain a 2β-substituent: 2β-hydroxy-3α-bromo derivative *XII* contains only the band of a free hydroxyl in its infrared spectrum so that it exists practically in the

TABLE I

Coupling Constants and Chemical Shifts of Ring A Protons

Measured at 100 MHz on a Varian HA-100 instrument in deuteriochloroform, unless stated otherwise; tetramethylsilane as internal standard; the three-spin systems were analysed as ABX systems, higher spin systems as first order spectra.

Compound	Substituent		Coupling constants					Chemical shifts, p.p.m.				
	2	3	$-J_{1\alpha,1\beta}$	$J_{1\alpha,2}$	$J_{1\beta,2}$	$J_{2,3}$	$J_{3,4\beta}$	1α-H	1β-H	2-H	3-H	4α-CH_3[a]
XI[b]		α-OH	[c]	[c]	[c]	~ 2·5; ~ 2·5	~ 2·5	[c]	[c]	[c]	3·63[d]	0·87[d]
XVIII		β-OH	[c]	[c]	[c]	~10; ~ 5	~10	[c]	[c]	[c]	3·07	0·95
IX	α-Br	β-OH	12·7	12·5	5·0	9·7	9·7	<1·70	2·41	4·27	3·21	1·05
XV	β-Br	α-OH	[c]	~5·4	~2·8	~ 2·7	~ 2·7	[c]	[c]	4·34	4·00	0·98
VI	α-Br	=O	12·8	13·4	6·6	—	—	<2·00	2·71	4·83	—	1·07
XVI	$=Br_2$	=O	16	—	—	—	—	2·85	3·38	—	—	1·30
XIX	β-Br	=O	[c]	[c,e]	[c,e]	—	—	~2·26	~2·26	4·76	—	1·12
XIX[f]	β-Br	=O	14·5	9·1	5·5	—	—	1·57	1·96	4·30	—	0·83
XX[g]	β-Br	=O	13·4	11·2	9·4	—	—	2·48	2·08	5·11	—	—
XXI[g]	β-Br	=O	13·6	11·2	9·5	—	—	2·50	2·08	5·10	—	—
XXII	β-Br	=O	15·4	6·5	2·6	—	—	2·07	2·38	4·45[h]	—	—

[a] Doublet, $J_{4\beta\ 23}$ ~7 Hz; [b] in a mixture of $CDCl_3$ and C_6H_6 (5 : 1); [c] undeterminable values; [d] in $CDCl_3$ the 3β-H signal is overlapped by the $C_{(28)}$—H signal (~3·70 p.p.m.), doublet of 4α-CH_3 is at 0·92 p.p.m.; [e] degenerated ABX spectrum, $\Sigma J_{1,2} = 15{\cdot}9$ Hz; [f] in C_6D_6; [g] the preparation of compounds *XX* and *XXI* has been described in ref.[13]; the observed values are within experimental errors and they agree with the data obtained in paper[10] from 60 MHz spectra of compound *XX*; [h] further splitting (~1·4 Hz) caused by long-range coupling with 4α-H.

chair form only, while in the derivative containing an additional 4β-methyl group the boat form prevails (~85%; see[12]). In 2β-bromo-3α-hydroxy derivative *XV* the values of the vicinal coupling constants $J_{1,2}$ and $J_{2,3}$ also correspond to the chair form. However, in the infrared spectrum a very weak band of bonded hydroxyl is present in addition to the strong band of a free hydroxyl, indicating a boat form. From the ratio of absorption intensities B_f/B_b (similarly as in paper[12]) it may be estimated that the content of the boat form at equilibrium is about 7% only. In 2β--bromo-3α-hydroxy derivatives which contain both the 4β and the 10β methyl group the ring A exists practically in the boat form only[6,12]. Hence the presence of both axial methyl groups in these bromohydrins has a decisive effect on the chair-boat equilibrium. If only a single one of the two is present (derivatives *XII*, *XV* and analogous derivatives of 5α-cholestane[6], 4,4-dimethyl-5α-estrane[5] and 9-methyl-*trans*-decalin[27]) then it is the chair form which predominates. In the derivatives mentioned the differences between the effects of single methyl groups cannot be determined because the equilibrium is in all instances shifted too far to the chair form side.

In dibromoketone *XVI* it is impossible to decide unambiguously from spectral data between the chair and the boat form; however, the strongly positive Cotton effect corresponds rather to the chair form. 2β-Bromo ketone *XIX* contains two well separated bands in the carbonyl region of its infrared spectrum; the stronger one

TABLE II

Frequencies and Intensities of OH Stretching Vibrations

Measured in $2-4 \cdot 10^{-3}$M solution in tetrachloromethane on a grating spectrophotometer Unicam SP 700.

Compound	Substituent 2	Substituent 3	ν(OH)[a] cm^{-1}	$\varepsilon^{(a)}$ $l\,mol^{-1}\,cm^{-1}$	$\Delta\nu_{1/2}^{(a)}$ cm^{-1}	$B \cdot 10^{-3}$ [b] $l\,mol^{-1}\,cm^{-2}$
XI	—	α-OH	f 3 633	63	19	1·9
XVIII	—	β-OH	f 3 632 f 3 624 sh f 3 613 sh	39	~35[c]	~2·1[c]
IX	α-Br	β-OH	b 3 587	52	25	2·0
X	α-Br	α-OH	b 3 583	53	28	2·3
XII	β-OH	α-Br	f 3 622[d]	87	20	2·7
XV[e]	β-Br	α-OH	f 3 628 b 3 577	82 5	18 23	2·3 0·18

[a] Accuracy ± 2 cm^{-1}, f free, b bonded, sh shoulder; [b] $B = \pi/2 \cdot \varepsilon^{(a)} \cdot \Delta\nu_{1/2}^{(a)}$; [c] without separation of overlapping bands; [d] the band is asymmetric towards lower frequencies; [e] after graphical separation.

TABLE III
Characteristic Spectral Parameters of 3-Oxo Derivatives

Compound	Substituents in the position 2	IR[a]		UV[b]		CD[c]		
		ν(CO) cm^{-1}	$\Delta\nu$(CO) cm^{-1}	λ nm	ε $l\ mol^{-1}\ .\ cm^{-1}$	λ nm	$\Delta\varepsilon$	Γ nm
III	—	1 712	—	286	28	292	+1·5	36
VI	α-Br	1 733	+21	285	42	289	+2·3	38
XVI	α-Br, β-Br	1 733	+21	301	116	303	+3·9	45
XIX	β-Br	1 717[d] 1 740[d]	+ 5 +28	[e]	[e]	[e]	[e]	[e]

[a] Measured on 0·5% solutions in tetrachloromethane on a UR-20 spectrophotometer calibrated in the carbonyl region with atmospheric water vapour, cell thickness 1 mm, precision $\pm 1\ cm^{-1}$; [b] measured in cyclohexane on a Unicam SP 700; [c] measured in dioxan on a Roussel-Jouan 185 dichrograph; [d] after graphical separation, $B_{1717}/B_{1740} = 1{\cdot}4$, $\varepsilon^{(a)}_{1717}/\varepsilon^{(a)}_{1740} = 1{\cdot}55$; [e] not measured.

which is shifted by $+5\ cm^{-1}$ in comparison with the unsubstituted ketone *III* may be assigned to the chair form of ring A with an axial bromine atom[28], and the weaker one shifted by $+28\ cm^{-1}$, may be assigned to the boat form (equatorial bromine atom). Under the assumption that the integrated absorption intensities are 25% lower in the case of equatorial bromo ketones than in axial bromo ketones[28] the population of the boat form (49% in CCl_4) was calculated from the ratio of the absorption intensities B of both bands. From the ratio of absorbances the values 46% was obtained under analogous assumptions. The population of the boat form was also calculated from the vicinal and geminal coupling constants of the protons in the positions 1 and 2 by a method based on the averaging of the coupling constants during a rapid interconversion of the two conformers (see also[12]). As starting values for pure conformers the coupling constants were used which were found for 2β-bromo-19β,28-epoxy-18α-oleanan-3-one (*XX*) and 2β-bromo-20β,28-epoxy-18α,19β*H*-ursan-3-one (*XXI*), having their A ring in boat form[10,11], and in 2β-bromo-5α-cholestan-3-one (*XXII*), existing according to its infrared spectrum in the chair form[2]. For the population of the boat form of 2β-bromo ketone *XIX* (in C_6D_6) the value 47% was obtained from $J_{1\alpha,1\beta}$, 55% from $J_{1\alpha,2}$, 43% from $J_{1\beta,2}$, and 48% from the sum of the last two constants ($\sum J_{1,2}$). For a solution in deuteriochloroform only $\sum J_{1,2}$ could be obtained from the spectrum, and the value obtained indicates 59% of the boat form.

The use of $\sum J_{1,2}$ for the estimation of the boat form population has two advantages: on the one hand this value may be obtained with great accuracy only from the signal 2α-H, and on the other the results are completely independent of the assignment of the 1α-H and 1β-H signals in any of the derivatives *XIX*—*XXII*. This assignement was carried out for bromo ketones *XX* and *XXI* according to ref.[10,29], for bromo ketone *XXII* on the basis of the rule that an axial hydrogen is more shielded, and for bromo ketone *XIX* on the basis of the $J_{1\alpha,2}$ and $J_{1\beta,2}$ values, taking care that these results should agree with those obtained from $\sum J_{1,2}$ and from $J_{1\alpha,1\beta}$. It should be further noted that the use of compounds *XX* and *XXI* as models for the boat form includes the assumption that the geometry of the boat form of the ring A in bromo ketones *XIX*, *XX* and *XXI* is identical. However, in view of the absence of the 4β-methyl-group the boat form in bromo ketone *XIX* may be more turned in the direction of the classical boat form with $C_{(2)}$ and $C_{(5)}$ in stem-stern position than in the case of derivatives *XX* and *XXI*. The ring A conformation in another model compound *i.e.* in 2β-bromo-5α-cholestan-3-one (*XXII*) is also problematical: its ^{1}H-NMR spectrum has already been described in references[3,4,30]. In view of the differences in the shape of the 2α-H signal and in the coupling constants in the mentioned papers we prepared bromo ketone *XXII* from 2β-bromo-5α-cholestan-3α-ol[2] in the same manner as in the case of bromo ketone *XIX*. The coupling constant values found by us agree with literature[30], the shape of the multiplet of 2α-H agrees with lit.[4], but both are different from the data in lit.[3]. The $\sum J_{1,2}$ value of derivative *XXII* (9·1 Hz) agrees with the value published for the analogous derivative of 9-methyl-*trans*-decalin[27] (9 Hz), but it is higher than in axial bromo ketones derived from tert-butylcyclohexane[31] and *trans*-decalin[32] (~6 Hz). These differences may be assigned partly to the ring deformation caused by 1,3-syn-axial interaction between the methyl group and the bromine atom, but they may also indicate that in 2β-bromo-5α-cholestan-3-one (*XXII*) 10 to 20% of the boat form is present at equilibrium. Therefore the above computed values for the boat form population of bromo ketone *XIX* may be hampered by an error amounting to up to 10%. In spite of this the agreement with the results obtained from the infrared spectrum — which are independent of these assumptions — is very good.

Therefore in non-polar solvents the chair and the boat forms of 2β-bromo ketone *XIX* occur at equilibrium in an approximately 1 : 1 ratio. In accordance with this are also the chemical shifts of 1α, 1β and 2α hydrogens which in bromo ketone *XIX* (in $CDCl_3$) represent just the arithmetical mean of the shifts found for the boat form (compounds *XX* and *XXI*) and the chair form (compound *XXII*). In analogous bromo ketones also containing in the ring A a single axial methyl group (derivatives of 5α-cholestane[2], 4,4-dimethyl-5α-estrane[5] and 9-methyl-*trans*-decalin[27]) the chair form highly predominates. In comparison with these derivatives the increase in the population of the boat form in bromo ketone *XIX* is probably caused by the presence of the 8β-methyl group which destabilizes the chair form of the ring A (see also[12]). If two axial methyl groups are present on ring A the equilibrium is shifted far to the boat form side[6,8–11,19].

The differences between various skeletons may also be observed in the stereochemistry of the opening of 2β,3β-epoxides with hydrobromic acid[5,13]. These epoxides both open normally according to the Fürst-Plattner rule, giving diaxial 2β--hydroxy-3α-bromo derivatives, and also anomalously under formation of diequatorial 2α-bromo-3β-hydroxy derivatives. In the first case the reaction takes place *via* the chair-type transition state, while in the second *via* the boat-type transition

state[5,6,8,13]. Therefore the ratio of the amounts of the formed "anomalous" and "normal" product is rather sensitive to such structural changes which affect the energy of the chair and the boat form of the ring A differently. In our recent papers we demonstrated[12,13,33] that the results obtained on the basis of this ratio are comparable with the results obtained from the data for the chair-boat equilibrium in bromohydrins, bromo ketones, diols, and similar compounds.

In the case of epoxide *VIII* the normal product *XII* prevails over the anomalous product *IX*. For the determination of their ratio infrared spectra were made use of, *i.e.* the OH stretching frequencies region: the diequatorial isomer *IX* contains a single band of a bonded hydroxyl, while the diaxial isomer *XII* has only a band of a free hydroxyl (Table II). On the basis of the intensities of the bands ($\varepsilon^{(a)}$ and *B*) in pure isomers *IX* and *XII* the content of the anomalous product *IX* was calculated ($23 \pm 5\%$) from the spectrum of the mixture obtained. Practically the same result ($25 \pm 10\%$) was obtained from optical rotation. For comparison the reaction of 2β,3β-epoxy-5α-cholestane with hydrobromic acid was also carried out, of which it is known[34] that it leads to a normal product (3α-bromo-5α-cholestan-2β-ol). According to thin-layer chromatography the anomalous product (2α-bromo-5α--cholestan-3β-ol) was formed in trace amount only. From the OH stretching region in the infrared spectrum of the crude mixture it was estimated that the content of the anomalous product should be lower than 5%. On the contrary, in 2β,3β-epoxides, containing 4α,4β and 10β-methyl groups, the anomalous product predominates (in the 19β,28-epoxy-18α-oleanane[13] series it is 90%, in the 4,4-dimethyl-5α-cholestane[6] and 8-lanostene[9] series it is 80%). In the 4,4-dimethyl-5α-estrane series 51% of the anomalous product[5] were found.

According to Francois and Levisalles[5] two factors are important for the stereochemistry of the opening of β-epoxides: *a*) prevention of the attack on $C_{(3)}$ due to two methyl groups in the position 4; *b*) syn-axial interactions developing between 4β and 10β methyl groups and the 2β-oxygen atom. Both factors are operative in the chair transition state and they act against the normal opening. In comparison with the derivatives containing 4α, 4β and 10β-methyl groups it may be seen that the elimination of the axial methyl group from the position 4β in derivative *VIII* causes the boat transition state to play a minor role. This is evidently due to the second factor – decrease in the number of syn-axial interactions on the β-side furthers the chair transition state. A higher proportion of the boat transition state in epoxide *VIII* in comparison with the analogous derivative of 5α-cholestane may be caused both by the first factor and by the destabilization of the chair transition state under the effect of the 8β-methyl group (see[12]). These results agree so far with those obtained on the basis of conformational equilibria of 2β-bromo ketones (see above). However, in comparison with 4,4-dimethyl-5α-estrane series an opposite effect appears during the opening of 2β,3β-epoxides than in 2β-bromo ketones: the boat transition state is preferred more in 4,4-dimethylestrane derivative than in epoxide *VIII*, while

in 2β-bromo-3-oxo derivatives the boat form is more populated in 24-nortriterpenoid derivative *XIX*. This phenomenon can be hardly explained on the basis of the two mentioned factors alone. Therefore we consider that in the opening of β-epoxides still another factor plays a role, *i.e.* a non-bonding interaction which appears in the case of the boat transition state between the formed 3β-hydroxy group and 10β-methyl group. In bromohydrins and diols this interaction destabilizes the boat form of the ring A strongly (ref.[12]). Although its magnitude in the transition state may be smaller than in the fundamental state it seems to us that this interaction plays an important role also in the opening of 2β,3β-epoxides with a 10β-methyl group. Hence the absence of the 10β methyl group in 4,4-dimethyl-5α-estrane results in a relative preference of the boat transition state.

EXPERIMENTAL

The melting points were determined on a Kofler block. Optical rotations were measured in chloroform (c 0·3—0·7) on an automatic polarimeter ETL-NPL (Bendix-Ericssson) with a ± 1—2° error. The infrared spectra were measured in chloroform on a UR-20 (Zeiss, Jena) spectrophotometer, the ultraviolet spectra were measured in cyclohexane on a Unicam SP 700 spectrophotometer. The reaction course and the purity of the samples was controlled with thin layer chromatography on silica gel according to Stahl (type 60) and on silica gel with 10% of silver nitrate. For column chromatography neutral alumina (Reanal, activity II) and neutral silica gel CH (70—200 μm) were used. For preparative thin-layer chromatography silica gel according to Stahl was used. Detection was carried out in ultraviolet light after spraying the plates with a 0·2% morin solution in methanol. Unless stated otherwise the working up of the reaction mixtures was carried out in the following manner: the mixture was diluted with water, extracted with ether or chloroform, the extract was washed with water, aqueous sodium hydrogen carbonate solution and water, and dried over sodium sulfate. The solvent was evaporated under reduced pressure. The identity of the compounds was confirmed by infrared spectra and mixture melting points. Samples for analysis were dried over phosphorus pentoxide at 100°C and 0·1—1 Torr for 8—16 hours.

19β,28-Epoxy-24-nor-18α-oleanan-3-one (*III*)

A) A crude mixture of epoxynitriles *II*, isomeric at $C_{(4)}$ (2·0 g; prepared according to ref.[35]), was dissolved in toluene (70 ml), freshly distilled boron trifluoride etherate (2·5 ml) was added to it, and the mixture was refluxed under nitrogen for 6 hours. After working up the residue was dissolved in benzene and chromatographed on alumina (20 g). Benzene eluted 1·70 g of chromatographically pure ketone *III* which after crystallization from chloroform–hexane had m.p. 215 to 216°C, $[\alpha]_D$ +82°. Yield 1·37 g. Lit.[14] gave m.p. 218—219·5°C, $[\alpha]_D$ +83°, lit.[36] gives m.p. 214—215°C, $[\alpha]_D$ +84°. When this experiment was reproduced repeatedly it was observed that working under nitrogen or distillation of boron trifluoride etherate is not indispensable for the achievement of high yields of ketone *III* (70—90%).

B) A solution of bromohydrin *X* (50 mg) and potassium hydroxide (150 mg) in ethanol (10 ml) was refluxed for 3 hours. After working up of the mixture the products were separated by preparative thin-layer chromatography on silica gel (benzene–ether 9 : 1). Ketone *III* (30 mg) was obtained, m.p. 214—216°C (chloroform–hexane), identical with the sample obtained under *A*).

Further an unidentified substance was obtained (5 mg) which contained an aldehyde group. IR spectrum: 2830, 2730, 1722 (HCO), 1036 (COC) cm^{-1}.

19β,28-Epoxy-24-nor-18α-olean-1-en-3-one (*IV*) and 19β,28-Epoxy-24-nor-18α-olean-4-en-3-one (*V*)

A) A solution of bromo ketone *VI* (50 mg) and anhydrous lithium chloride (250 mg) in dimethylformamide (7 ml) was refluxed for 2·5 hours. After working up the mixture of products was separated by preparative thin-layer chromatography on silica gel layers (benzene–ether 9 : 1). Ketone *IV* (25 mg) was obtained, melting at 236—238°C (chloroform–methanol), $[\alpha]_D$ +81°. IR spectrum: 1678 (CO), 1036 (COC) cm^{-1}. UV spectrum: 224 nm (log ε 3·96). For $C_{29}H_{44}O_2$ (424·6) calculated: 82·02% C, 10·44% H; found: 81·96% C, 10·36% H. Further, ketone *V* (10 mg) was also obtained, m.p. 238—241°C (hexane), $[\alpha]_D$ +128°. IR spectrum: 1663, 1613 (CO—C=C), 1037 (COC) cm^{-1}. UV spectrum: 243 nm (log ε 4·16). For $C_{29}H_{44}O_2$ (424·6) calculated: 82·02% C, 10·44% H; found: 82·10% C, 10·28% H.

B) A solution of bromo ketone *VI* (40 mg) in collidine (5 ml) was refluxed under nitrogen for 11·5 hours. The precipitated collidine hydrobromide was filtered off, the filtrate was diluted with ether, the solution was washed with dilute hydrochloric acid and further worked up in the conventional manner. After chromatography (as under *A*) 20 mg of ketone *IV* and 10 mg of ketone *V* were obtained. Both derivatives were identical with the samples described under *A*).

C) Hydrobromic acid solution in acetic acid (31% w/v; 0·5 ml) was added to a solution of bromo ketone *VI* (50 mg) in chloroform (12 ml) and the mixture was allowed to stand at room temperature for 19 hours. After working up as usual and preparative thin-layer chromatography and crystallization from chloroform–methanol ketone *V* was obtained (15 mg), identical with the sample described under *A*).

2α-Bromo-19β,28-epoxy-24-nor-18α-oleanan-3-one (*VI*)

A) A solution of bromine (96 mg) in acetic acid (2 ml) was added to a solution of enol acetate *VII* (200 mg) in a mixture of chloroform (12 ml), acetic acid (25 ml), and pyridine (2 ml).The mixture was allowed to stand in a dark place at room temperature for 4 hours and it was then worked up. The residue was chromatographed on silica gel (20 g). Benzene–ether mixture (9 : 1) eluted bromo ketone *VI* (180 mg), m.p. 191—199°C (decomposition; chloroform–hexane), $[\alpha]_D$ +75°. IR spectrum: 1729 (CO), 1034 (COC) cm^{-1}. For $C_{29}H_{45}BrO_2$ (505·6) calculated: 68·89% C, 8·97% H; found: 68·75% C, 8·95% H.

B) A solution of bromine (80 mg) and anhydrous sodium acetate (41 mg) in acetic acid (21 ml) was added dropwise under stirring over 45 minutes to a solution of ketone *III* (200 mg) in acetic acid (25 ml) to which a drop of 31% hydrobromic acid in acetic acid was added and the mixture was further stirred for 15 minutes and then worked up. The crude product contained according to thin layer chromatography traces of dibromo ketone *XVI*. After crystallization from a mixture of chloroform and hexane bromoketone *VI* (220 mg) was obtained which was identical with a sample described under *A*); m.p. 195—199°C (decomp.), $[\alpha]_D$ +73°.

3-Acetoxy-19β,28-epoxy-24-nor-18α-olean-2-ene (*VII*)

A solution of ketone *III* (100 mg) and *p*-toluenesulfonic acid (30 mg) in isopropenyl acetate (9 ml) was refluxed for 7 hours, During this period 1 ml of solvent was distilled off gradually. Almost the whole remaining isopropenyl acetate was then distilled off over one hour and the residue was worked up. Crystallization from hexane gave enolacetate *VII* (70 mg), m.p. 243 to

245°C, $[\alpha]_D$ +48°. IR spectrum: 1754, 1246, (CH_3COO), 1697 (C=C), 1035 (COC) cm^{-1}. For $C_{31}H_{48}O_3$ (468·7) calculated: 79·43% C, 10·32% H; found: 79·21% C, 10·11% H.

2β,3β;19β,28-Diepoxy-24-nor-18α-oleanane (*VIII*)

A solution of bromohydrin *IX* (220 mg) and potassium hydroxide (250 mg) in ethanol (50 ml) was refluxed for 3 hours. After working up the mixture the product was purified by preparative thin-layer chromatography on silica gel in benzene–ether 9 : 1 and by crystallization from chloroform–hexane. Yield, 100 mg of epoxide *VIII*, m.p. 226—228°C, $[\alpha]_D$ +56°. IR spectrum: 1036 (COC) cm^{-1}. For $C_{29}H_{46}O_2$ (426·7) calculated: 81·63% C, 10·87% H; found: 81·43% C, 10·98% H.

2α-Bromo-19β,28-epoxy-24-nor-18α-oleanan-3β-ol (*IX*) and 2α-Bromo-19β,28-epoxy-24-nor-18α-oleanan-3α-ol (*X*)

Sodium borohydride (65 mg) was added to a solution of bromoketone *VI* (400 mg) in a mixture of benzene (30 ml) and methanol (30 ml) and the reaction mixture was stirred for 2 hours. After pouring it into dilute hydrochloric acid it was worked up in the conventional manner. Preparative thin-layer chromatography of the mixture on silica gel (with benzene–ether 9 : 1) gave 170 mg of the less polar bromohydrin *X* and 110 mg of the more polar bromohydrin *IX*. After crystallization from a mixture of chloroform–methanol bromohydrin *IX* had m.p. 207—209°C or 235—238°C (with a change of crystal habit at about 140°C); $[\alpha]_D$ +51°. IR spectrum: 3595 (OH), 1036 (COC) cm^{-1}. For $C_{29}H_{47}BrO_2$ (507·6) calculated: 68·62% C, 9·33% H; found: 68·50% C, 9·12% H. Bromohydrin *X* had m.p. 235—236°C (methanol), $[\alpha]_D$ +56°. IR spectrum: 3587 (OH), 1036 (COC) cm^{-1}. For $C_{29}H_{47}BrO_2$ (507·6) calculated: 68·62% C, 9·33% H; found: 68·49% C, 9·22% H.

19β,28-Epoxy-24-nor-18α-oleanan-3α-ol (*XI*) and 19β,28-Epoxy-24-nor-18α-oleanan-3β-ol (*XVIII*)

A) Sodium borohydride (80 mg) in methanol (10 ml) was added to a solution of ketone *III* (440 mg) in benzene (10 ml) and the mixture was stirred for one hour. After acidification with dilute hydrochloric acid it was worked up as usual. The residue was dissolved in benzene and chromatographed on silica gel (25 g). Benzene–ether (19 : 1) mixture eluted hydroxy derivative *XI* (70 mg), m.p. 249—251°C (chloroform–methanol), $[\alpha]_D$ +46°. IR spectrum: 3635 (OH), 1035 (COC) cm^{-1}. For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·04% C, 11·11% H. With benzene–ether mixture 14 : 1 hydroxy derivative *XVIII* (320 mg) was eluted which had m.p. 295—296°C (chloroform–methanol), $[\alpha]_D$ +66°. IR spectrum: 3629, 3420 (OH), 1038 (COC) cm^{-1}. For $C_{29}H_{48}O_2$ (428·7) calculated: 81·25% C, 11·29% H; found: 81·08% C, 11·23% H.

B) A mixture of bromohydrin *X* (60 mg), calcium carbonate (10 mg), and 10% palladium on charcoal (500 mg) in ethanol (100 ml) was hydrogenated under shaking for 20 hours. After working up, preparative chromatography on a silica gel thin layer in benzene–ether (9 : 1), and crystallization from chloroform–methanol, hydroxy derivative *XI* (32 mg) was obtained, which was identical with the sample described under *A*); m.p. 249—251°C.

3α-Bromo-19β,28-epoxy-24-nor-18α-oleanan-2β-ol (*XII*)

A) A mixture of epoxide *VIII* (100 mg), chloroform (5 ml) and 48% hydrobromic acid (4 ml) was stirred for 2 hours. After working up the mixture of bromohydrins *IX* and *XII* obtained had

$[\alpha]_D$ +66° and it was separated by preparative thin-layer chromatography on silica gel in hexane–ether 3 : 2. The yields were 20 mg of bromohydrin *IX*, identical with the sample described above, and 55 mg of bromohydrin *XII*, m.p. 202—204°C (methanol), $[\alpha]_D$ +71°. IR spectrum: 3620, 3400 (OH), 1032 (COC) cm^{-1}. For $C_{29}H_{47}BrO_2$ (507·6) calculated: 68·62% C, 9·33% H; found: 68·42% C, 9·18% H.

B) N-Bromosuccinimide (300 mg) was added to a solution of olefin *XIII* (300 mg) in a mixture of chloroform (18 ml), dimethyl sulfoxide (9 ml) and water (0·3 ml) and the reaction mixture was allowed to stand in a dark place at room temperature for 23 hours. After the conventional work-up the product was chromatographed on silica gel (30 g; elution with benzene–ether 19 : 1) and then crystallized from a dichloromethane–light petroleum mixture. The yield of bromohydrin *XII* was 100 mg, m.p. 201—204°C; it was identical with the sample described under *A*). Further chromatographic fractions did not contain bromine and they were not identified.

19β,28-Epoxy-24-nor-18α-olean-2-ene (*XIII*)

A mixture of bromohydrins *IX* and *X* (400 mg), obtained on reduction of bromo ketone *VI* (see above), was dissolved in acetic acid (50 ml). The solution was refluxed for one hour under gradual addition of 2 g of zinc dust. The mixture was then worked up and the residue chromatographed on silica gel (30 g). Benzene eluted olefin *XIII* (250 mg), m.p. 209—211°C (chloroform–methanol), $[\alpha]_D$ +43°. IR spectrum: 1661 (C=C), 1035 (COC) cm^{-1}. For $C_{29}H_{46}O$ (410·7) calculated: 84·81% C, 11·29% H; found: 84·56% C, 11·30% H.

2α,3α; 19β,28-Diepoxy-24-nor-18α-oleanane (*XIV*)

A) A solution of olefin *XIII* (220 mg) and 3-chloroperoxybenzoic acid (120 mg) in chloroform (20 ml) was allowed to stand at 0°C for 4 hours. After working up and crystallization from a mixture of chloroform and methanol epoxide *XIV* was obtained (150 mg), m.p. 225—226°C, $[\alpha]_D$ +27°. IR spectrum: 1036 (COC) cm^{-1}. For $C_{29}H_{46}O_2$ (426·7) calculated: 81·63% C, 10·87% H; found: 81·35% C, 11·02% H.

B) A solution of bromohydrin *XV* (50 mg) and potassium hydroxide (100 mg) in ethanol (50 ml) was refluxed for 3 hours. After working up and crystallization from chloroform–hexane epoxide *XIV* (15 mg) was obtained, m.p. 224—226°C, identical with a sample described under *A*.

C) A solution of toluenesulfonylhydrazine (80 mg) in methanol (10 ml) was added to a solution of ketone *III* (170 mg) in benzene (10 ml) and the mixture was refluxed for 3 hours and then worked up. The residue was chromatographed on silica gel (18 g). Benzene–ether mixture (9 : 1) eluted 120 mg of *p*-toluenesulfonylhydrazone. 100 mg of this derivative were dissolved in 1,2-dimethoxyethane (25 ml), lithium aluminum hydride (400 mg) was added to it and the mixture was refluxed under nitrogen for 25 hours. Excess hydride was decomposed with ethyl acetate; the mixture was acidified with dilute hydrochloric acid and worked up in the usual manner. A mixture of olefin *XIII* and a saturated derivative which was not characterized was formed, which was submitted to epoxide formation as under *A*). From the obtained mixture epoxide *XIV* (20 mg), m.p. 224—226°C (chloroform–methanol), was isolated by preparative thin-layer chromatography on silica gel (with benzene–ether 14 : 1). It was identical with the preparation described under *A*).

2β-Bromo-19β,28-epoxy-24-nor-18α-oleanan-3α-ol (*XV*)

A mixture of epoxide *XIV* (150 mg), chloroform (25 ml) and 48% of hydrobromic acid (6 ml) was stirred for 2 hours. After working up and crystallization from chloroform–methanol bromo-

hydrin *XV* (90 mg) was obtained, m.p. 228—231°C, $[\alpha]_D$ +78°. IR spectrum: 3622 (OH), 1036 (COC) cm^{-1}. For $C_{29}H_{47}BrO_2$ (507·6) calculated: 68·62% C, 9·33% H; found: 68·80% C, 9·47% H.

2,2-Dibromo-19β,28-epoxy-24-nor-18α-oleanan-3-one (*XVI*)

During repeated preparations of bromo ketone *VI* from larger amounts of ketone *III* (1 to 1·5 g) the obtained mixture contained in addition to bromo ketone *VI* small amounts of ketone *III* and dibromo ketone *XVI*. Using chromatography on silica gel (elution with benzene) dibromo ketone *XVI* was isolated (8—20%) which after crystallization from chloroform–hexane had m.p. 196—198°C (decomp.), $[\alpha]_D$ +86°. IR spectrum: 1732 (CO), 1037 (COC) cm^{-1}. For $C_{29}H_{44}Br_2O_2$ (584·5) calculated: 59·59% C, 7·59% H; found: 59·50% C, 7·49% H.

2-Bromo-19β,28-epoxy-24-nor-18α-olean-1-en-3-one (*XVII*)

A) A solution of dibromo ketone *XVI* (150 mg) and anhydrous lithium chloride (750 mg) in dimethylformamide (15 ml) was refluxed for 2·5 hours. After working up and crystallization from chloroform–methanol and from hexane derivative *XVII* (30 mg) was obtained, m.p. 230 to 235°C (decomposition), $[\alpha]_D$ +63°. IR spectrum: 1698, 1601 (CO—C=C), 1037 (COC) cm^{-1}. UV spectrum: 256 nm ($\log \varepsilon$ 3·83). For $C_{29}H_{43}BrO_2$ (503·6) calculated: 69·17% C, 8·61% H; found: 69·01% C, 8·56% H.

B) A solution of dibromo ketone *XVI* (50 mg) in collidine (5 ml) was refluxed under nitrogen for 11·5 hours. The separated collidine hydrobromide was filtered off, the filtrate was diluted with ether and the ethereal solution washed with dilute hydrochloric acid and worked up in the usual manner. After crystallization from ether–light petroleum mixture derivative *XVII* (20 mg) was obtained, m.p. 231—234°C (decomposition), identical with the preparation described under *A*). Derivative *XVII* was also obtained from dibromo ketone *XVI* on reaction with hydrobromic acid in acetic acid.

2β-Bromo-19β,28-epoxy-24-nor-18α-oleanan-3-one (*XIX*)

Sodium dichromate dihydrate (110 mg) and sodium acetate (60 mg) dissolved in acetic acid (15 ml) were added to a solution of bromohydrin *XV* (90 mg) in acetic acid (50 ml) and the mixture was allowed to stand at room temperature for 3 hours. After working up and crystallization from ether–hexane bromo ketone *XIX* (40 mg) was obtained which decomposed between 170 and 210°C (the decomposition point depends on the rate of heating and it is not reproducible). During chromatography on silica gel, crystallization from polar solvents or standing in a chloroform solution a rapid isomerization takes place to 2α-isomer *VI*. IR spectrum: 1737, 1722 (CO), 1036 (COC) cm^{-1}. For $C_{29}H_{45}BrO_2$ (505·6) calculated: 68·89% C, 8·97% H; found: 68·52% C, 8·73% H.

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