# REACTION OF LITHIUM ALUMINUM HYDRIDE WITH 4,4-DIMETHYL-4a,5-EPOXY-A-HOMOCHOLESTANE DERIVATIVES AND MASS SPECTRAL FRAGMENTATION OF SOME DEGRADATION PRODUCTS*

Helena VELGOVÁ and Antonín TRKA

*Institute of Organic Chemistry and Biochemistry, Czechoslovak Academy of Sciences, 166 10 Prague 6*

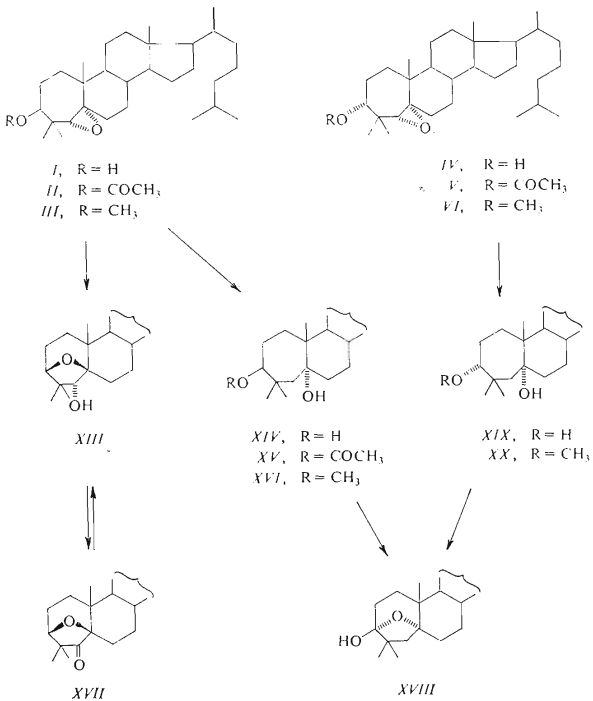
Received August 14th, 1981

Reductive opening of the epoxide ring of stereoisomeric 4,4-dimethyl-4a,5-epoxy-A-homocholestane derivatives with oxygen containing substituent (OH, $OCOCH_3$, $OCH_3$) in the position 3 was investigated. In the absence of other directing effects, than the stereoelectronic ones, the epoxide ring of 4aα,5α-epoxides is opened at the side of the less substituted carbon $C_{(4a)}$, under formation of 5α-hydroxy derivatives, while in the case of 4aβ,5β-epoxides both the cleavage of the $C_{(4a)}$—O bond, leading to the formation of 5β-hydroxy derivatives, and the cleavage of the $C_{(5)}$—O bond, leading to the formation of 4aβ-hydroxy-5,6-unsaturated derivatives take place. The participation of the substituent in the position 3 leads to an abnormal cleavage both in 4aα,5α- and 4aβ,5β-epoxides, *i.e.* to the cleavage of the $C_{(5)}$—O bond under formation of 3,5-epoxides. The effect of the character of the substituent in the position 3 on the direction of the reductive cleavage of the epoxide ring is also discussed from the point of view of conformational and electronic effects. In mass spectrometry the main product of the fragmentation of the molecular ions of the 4a-hydroxy-3,5-epoxides *XIII* and *XXV* and the 4a-ketones *XVII* and *XXVIII* is the ion $[C_{23}H_{40}O]^{+\cdot}$ which is formed after the breaking of the $C_{(3)}$—O bond by the splitting off of the ring A. The fragmentation of the molecular ion of the semi-ketal *XVIII* is determined by the cleavage of the epoxide bond O—$C_{(5)}$.

In our preceding paper[1] we found that the hydrogenolytic opening of the 4a,5-epoxide ring of stereoisomeric 3-acetoxy-4,4-dimethyl-4a,5-epoxy-A-homocholestanes in acetic acid takes place exclusively at the side of the tertiary carbon atom $C_{(5)}$ under formation of 4a-hydroxy-5,6-unsaturated derivatives. We were interested in the way the 4a,5-epoxide ring was opened in these derivatives under neutral conditions, where it may be supposed that an $S_N2$ mechanism is involved and thus the tendency to a cleavage on a more substituted carbon atom should be smaller[2]. This paper deals with the reductive opening of the 4a,5-epoxide ring of 4,4-dimethyl-4a,5-epoxy-A-homocholestane derivatives, carrying an oxygen-containing substituent ($OCOCH_3$, OH, $OCH_3$) in the position 3, with lithium aluminum hydride.

* Part CCLXX in the series On Steroids; Part CCLXIX: This Journal *47*, 1503 (1982).

The preparation of starting epoxides *I*, *II*, *IV*, *V*, *VII*, *VIII*, *X* and *XI* was described earlier[3]. Epoxides *III*, *VI*, *IX* and *XII* with a methoxy group in the position 3 were prepared on reaction of 3-hydroxy epoxides *I*, *IV*, *VII* and *X* with methyl iodide and potassium. The reactions of epoxides *I*–*XII* with lithium aluminum hydride were carried out in boiling dioxane and the proportion of the main products of cleavage of the 4a,5-epoxide ring in epoxides *I*–*XII* in the reaction mixtures is given in Table I.




In the $^1$H NMR spectra of 3,5-epoxides *XIII* and *XXV* (Table II) the signal of one CH—OH proton is evident, which appears as a singlet after exchange with $C^2H_3$. $COO_2H$, and the signal of one CH—O proton, which appears as a broad doublet. The oxidation of the 3,5-epoxide *XIII* with chromium trioxide in pyridine afforded

ketone *XVII*, while the oxidation of the 3,5-epoxide *XXV* afforded ketone *XXVIII*. Hence the structure of 4,4-dimethyl-3β,5-epoxy-A-homo-5β-cholestan-4aα-ol may be assigned to compound *XIII* and the structure of 4,4-dimethyl-3α,5-epoxy-A-homo--5α-cholestan-4aβ-ol to compound *XXV*. In the $^1$H-NMR spectra of 5-hydroxy derivatives *XIV*, *XIX*, *XVI*, *XX*, *XXII*, *XXIV* and *XXVI* (Table II) only the signal of the proton on carbon $C_{(3)}$ is evident, which is in agreement with the tertiary character of the 5-hydroxyl group. In the case of 3-methoxy derivative *XVI*, *XX* and *XXIV* their structure was confirmed by methylation of diols *XIV*, *XIX*, and *XXII* with methyl iodide and potassium. Oxidation of diols *XIV* and *XIX* with chromium trioxide in pyridine afforded the same semiketal *XVIII*. A similar participation of the 5-hydroxy group in the oxidation was also observed in the case of the oxidation of A-homocholestane-3,4a,5-triols[4]. In the $^1$H-NMR spectra of 4a-hydroxy--5,6-unsaturated derivatives *XXIII* and *XXVII* (Table II) the signals of one CH—OH proton and of one olefinic proton are evident, which appear, in agreement with the proposed structure, as a singlet and a multiplet. The allylic alcohols *XXI*, *XXX* and *XXXI* have been described earlier[1]. In the $^1$H-NMR spectrum of 3,5-epoxide *XXIX* (Table II) the signal of a single CH—O proton appears, but on the basis of its shape it is impossible to assign the α- or the β-configuration to the epoxide ring unambiguously. Since this epoxide *XXIX* is not identical with the known, 4,4-dimethyl-3α,5-

TABLE I

Yields (% of total yield) of the main products of reductive opening of epoxides *I*—*XII*

| Epoxide | 4a,5-Epoxide | 3,5-Epoxide | 5-Hydroxy derivative | 4a-Hydroxyl $\Delta^5$-derivative | Total yield % |
|---|---|---|---|---|---|
| *I* | 4 (*I*) | 89 (*XIII*) | 7 (*XIV*) | — | 94 |
| *II* | 24 (*I*) | 31 (*XIII*) | 45 (*XIV*) | — | 96 |
| *III* | 90 (*III*) | — | 10 (*XVI*) | — | 100 |
| *IV* | 48 (*IV*) | — | 52 (*XIX*) | — | 96 |
| *V* | 21 (*IV*) | — | 79 (*XIX*) | — | 100 |
| *VI* | 18 (*VI*) | — | 69 (*XX*) | — | 92 |
| | 13 (*IV*) | | | | |
| *VII* | 90 (*VII*) | — | 3 (*XXII*) | 7 (*XXI*) | 96 |
| *VIII* | 79 (*VII*) | — | 6 (*XXII*) | 15 (*XXI*) | 73 |
| *IX* | 25 (*IX*) | — | 37 (*XXIV*) | 38 (*XXIII*) | 84 |
| *X* | — | 91 (*XXV*) | 9 (*XXVI*) | — | 90 |
| *XI* | 20 (*X*) | 30 (*XXV*) | 50 (*XXVI*) | — | 98 |
| *XII* | 23 (*XII*) | 24 (*XXV*) | — | 53 (*XXVII*) | 83 |

-epoxy-A-homo-5α-cholestane[5], the structure of 4,4-dimethyl-3β,5-epoxy-A-homo-5β-cholestane may be assigned to this epoxide *XXIX*. This structure is also supported by the fact that epoxide *XXIX* is formed on reaction of lithium aluminum hydride with diol *XXVI* in boiling dioxane, while 4,4-dimethyl-3α,5-epoxy-A-homo-5α-cholestan-4aβ-ol (*XXV*) is stable against reduction under the same conditions. Epoxide *XXIX* is thus a product of reductive splitting off of the 3α-hydroxyl group and subsequent intramolecular cyclization.

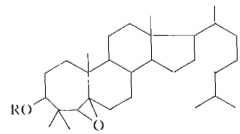
The reductive opening of the epoxide ring of asymmetrically substituted steroid epoxides takes place in agreement with the assumed $S_N2$ mechanism, where it is possible, on the least substituted carbon atom under formation of diaxially substituted products[6]. Thus in the case of 4α,5-epoxides of 4,4-dimethyl-A-homocholestane series the cleavage according to Markovnikov should lead preferentially to the cleavage of the $C_{(4a)}$—O bond. A study of Dreiding models showed that both in the case of 4aα,5α- and 4aβ,5β-epoxides the rule of the diaxial cleavage could be fulfilled owing to the flexibility of the seven-membered ring A not only by the cleavage

TABLE II

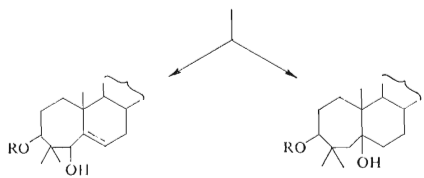
$^1$H-NMR Data of the products of reductive opening of epoxides *I*—*XI*. The spectra were measured in deuteriochloroform using tetramethylsilane as internal reference. The chemical shifts are given in ppm, δ-scale. The coupling constants and the half-widths $W_{1/2}$ are given in Hz. The following abbreviations were used for the characterization of the signals: d doublet, bd broad doublet, mt multiplet, s singlet

| Compound | $C_{(3)}$—H | $C_{(4a)}$—H | $C_{(6)}$—H |
|---|---|---|---|
| *XIII*[a] | 3·59 (bd, $W_{1/2}$ = 6) | 3·68 (d, $J_{H,OH}$ = 3·6)<br>3·68 (s)[c] | — |
| *XIV*[b] | 3·93 (mt) | — | — |
| *XVI*[b] | 3·25 (mt) | — | — |
| *XIX*[b] | 3·47 (mt) | — | — |
| *XX*[b] | 2·98 (mt) | — | — |
| *XXII*[b] | 3·68 (mt) | — | — |
| *XXIII*[b] | 3·025 (mt) | 3·83 (s) | 5·30 (mt) |
| *XXIV*[b] | 2·83 (mt) | — | — |
| *XXV*[a] | 3·60 (bd, $W_{1/2}$ = 7) | 3·52 (d, $J_{H,OH}$ = 3·2)<br>3·52 (s)[c] | — |
| *XXVI*[b] | 3·70 (mt) | — | — |
| *XXVII*[b] | 3·01 (mt) | 3·83 (s) | 5·41 (mt) |
| *XXIX*[b] | 3·54 (mt) | — | — |

[a] The spectra were measured on a Varian XL 200 instrument; [b] The spectra were measured on a Tesla B 476 (60 MHz) instrument. [c] The values were obtained after exchange in $C^2H_3.COO_2H$.




*VII*, R = H
*VIII*, R = $COCH_3$
*IX*, R = $CH_3$

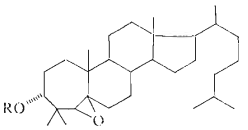



*XXI*, R = H
*XXIII*, R = $CH_3$

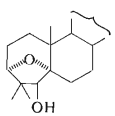
*XXII*, R = H
*XXIV*, R = $CH_3$

of the $C_{(4a)}$—O bond but also by the cleavage of the $C_{(5)}$—O bond. In the case of 4aα,5α-epoxides the cleavage of the $C_{(5)}$—O bond should lead, however, to the formation of 4,4-dimethyl-A-homo-5β-cholestane derivatives in which the 5β-hydrogen atom and the hydroxyl group in the position 4aα could be oriented *trans*-diaxially, but with respect to the ring B the 5β-hydrogen atom would assume a quasi-equatorial conformation. Similarly the 5β-hydroxy derivatives with *cis*-annelated rings A and B would be formed during the cleavage of the $C_{(4a)}$—O bond in the case of 4aβ,5β-epoxides. Hence, it may be assumed that in the case of 4aα,5α-epoxides *I*–*VI*, the $C_{(4a)}$—O bond will be split in the absence of other directing effects preferentially while in the case of 4aβ, 5β-epoxides *VII*–*XII* both the cleavage of the $C_{(4a)}$—O and the $C_{(5)}$—O bond might take place.

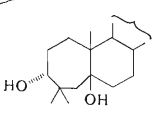
As evident from Table I, in the case of 3α-substituted 4aα,5α-epoxides *IV*–*VI* the $C_{(4a)}$—O bond indeed is cleaved exclusively (under formation of 5α-hydroxy derivatives *XIX* and *XX*), while in the case of 3β-substituted 4aβ,5β-epoxides *VII*–*IX* both the $C_{(4a)}$—O bond and the $C_{(5)}$—O bond are split under formation of 5β-hydroxy derivatives *XXII* and *XXIV* or allylic alcohols *XXI* and *XXIII*, respectively. However, the reactivity of the epoxide ring is very low in the case of epoxides *VII* and *VIII* and the cleavage of the $C_{(5)}$—O bond is weakly preferred. The introduction of the methoxy group into position 3β (epoxide *IX*) leads to a substantial increase of the reactivity of the epoxide ring, the cleavage of the $C_{(4a)}$—O and the $C_{(5)}$—O bond being



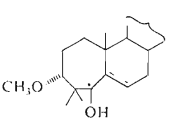

*X*, R = H
*XI*, R = $COCH_3$
*XII*, R = $CH_3$



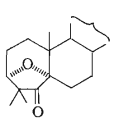

*XXV*



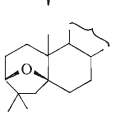

*XXVI*




*XXVII*




*XXVIII*




*XXIX*

operative approximately to the same extent. The formation of the allylic alcohols, observed during the reductive opening of the epoxide ring with lithium aluminum hydride also earlier[7,8], is in the case of epoxides *VII*–*IX* probably caused by the steric hindrance of the access of the relatively bulky nucleophile from the α-side of the cyclic system to the carbon atom $C_{(5)}$. Hover in the case of 3β-substituted 4aα,5α-epoxides *I*–*III* and 3α-substituted 4aβ,5β-epoxides *X*–*XII*, where the substituent in the position 3 may occur as a participating group in addition to the normal cleavage of the 4a,5-epoxide ring (*i.e.* the cleavage of the $C_{(4a)}$—O bond in the case of 4aα,5α-epoxides and the cleavage of the $C_{(4a)}$—O and the $C_{(5)}$—O bonds in the case of 4aβ,5β-epoxides – as described above) an abnormal cleavage also takes place, *i.e.* the cleavage of the $C_{(5)}$—O bond, leading to the formation of 3,5-epoxides *XIII* and *XXV*. The ratio between the normal and the abnormal cleavage is distinctly

affected by the character of the substituent in the position 3. The abnormal cleavage is practically the only way of reductive opening of the epoxide ring in the case of 3--hydroxy epoxides *I* and *X*. The introduction of an acetoxy group into position 3 (epoxides *II* and *XI*) leads to a substantial impairment of the abnormal cleavage and the normal cleavage of the $C_{(4a)}$—O bond is weakly preferred. An introduction of a methoxy group into position 3 (epoxides *III* and *XII*) leads – in the case of 4aα,5α-epoxide – to a complete suppression of the abnormal cleavage and to a distinct decrease of the reactivity of the epoxide ring, and in the case of the 4aβ,5β-epoxide *XII* to a distinct impairment of the abnormal cleavage of the $C_{(5)}$—O bond in favour of the normal cleavage of the $C_{(5)}$—O bond.

The study of Dreiding models showed that the most favourable conformations of the seven-membered ring A of epoxides *I*–*III* and *X*–*XII* for the participation of the substituent in the position 3 in the reductive opening of the 4a,5-epoxide ring are the conformations *A* and *B* in which the 3-substituent assumes a quasiaxial conformation (Fig. 1). The highest ability of the participation in the reductive opening of the 4a,5-epoxide ring by the $5(0)^n$ process (for notation see ref.[9]) is observed as already said above in the hydroxyl group. The decrease of the ability of the acetoxy group to participate in the reductive cleavage of the 4a,5-epoxide ring by the $5(0)^n$ process could be due either to the decreased electronic density of the ether--oxygen leading to its decreased nucleophilicity, by the competitive participation of the carbonyl oxygen of the ester group by the $6(0)^{\pi,n}$ process which would lead

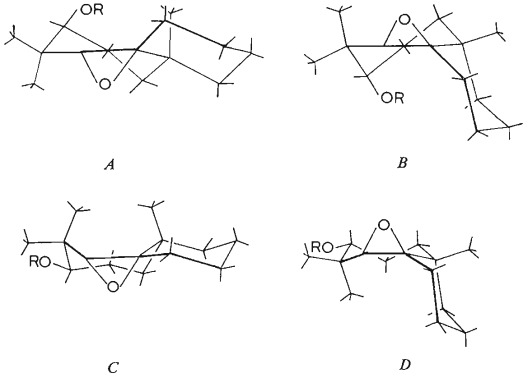
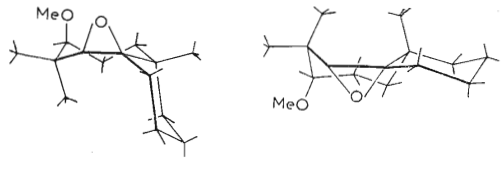



FIG. 1
Conformations of the ring A of 4aα,5α-epoxides *I*–*III* and 4aβ,5β-epoxides *X*–*XII*

to the formation of 5-hydroxy derivatives or by conformational control of the direction of the reductive cleavage of the 4a,5-epoxide ring[10]. Since the 3-acetoxy epoxides *II*, *V*, *VIII* and *XI* may be easily and quantitatively converted to corresponding 3-hydroxy epoxides, *I*, *IV*, *VII* and *X* on reaction with lithium aluminum hydride in ether at room temperature, it may be assumed that under the given conditions of reduction, *i.e.* in boiling dioxane, the acetoxy group will be more easily attacked with lithium aluminum hydride than the epoxide ring. However in the primarily formed Al-salt the relatively bulky solvated alkoxyaluminum group could have the tendency to assume preferentially the energetically more advantageous quasiequatorial conformation, for example in *C* and *D* conformations of the A-ring (Fig. 1). We believe that in the case of acetoxy epoxides *II* and *XI* the direction of the reductive cleavage is directed predominantly by conformational effects, *i.e.* that the nucleophilic reagent reacts with the equilibrium mixture of the conformers in which the conformers with a quasiequatorial substituent in the position 3 are weakly preferred. In the case of epoxides *III* and *XII* the introduction of a methoxy group into position 3 results, as already said, in an inhibition of the cleavage of the $C_{(4a)}$—O bond, which may be explained by the −I effect of the methoxy group, which will be both in 4aα,5α-epoxides and in 4aβ,5β-epoxides most pronounced on the carbon atom $C_{(4a)}$. Since in the case of 4aα,5α-epoxide *III* the formation of epoxide *XIII* was not observed, we consider that epoxide *XXV*, formed in a small amount on reductive opening of 4aβ,5β-epoxide *XII*, is rather a product of $5(0)^n$ participation of the 3α-hydroxy group formed primarily by reductive cleavage of the ether bond of the methoxy group. This is also supported by the fact that in the case of 3α-methoxy-4aα,5α-epoxide *VI* a reductive cleavage of the ether bond of the methoxy group does take place to a small extent (Table I).

However, in contrast to this a suitably oriented methoxy group can increase the reactivity of the epoxide ring, as observed in the case of 3β-methoxy-4aβ,5β-epoxide *IX*. Quite recently the view was expressed[11] that in reduction with $LiAlH_4$ the cation $Li^+$ plays an important role, *i.e.* it catalyses the opening of the epoxide ring with the nucleophilic anion $AlH_4^-$ by coordination with the epoxide oxygen. Owing to its flexibility the seven-membered ring A of epoxide *IX* may assume such a conformation, for example *E* (Fig. 2), in which the 3β-methoxy group is in quasiaxial conformation enabling a through-space interaction[12] of the free electron pair of the methoxy group oxygen with the epoxide oxygen which would lead to an increase of the electron density on the epoxide oxygen and hence to a facilitation of its coordination with the cation $Li^+$ and to an increase of reactivity of the 4a,5-epoxide ring. The increase in the reaction rate under the effect of the *syn*-methoxy group, which was also explained by through-space orbital interactions was observed, for example, in addition reactions to double bonds[13,14]. Similarly as in the case of 3α-methoxy-4aα,5α-epoxide *VI* the −I effect of the methoxy group does not play a distinct role in the case of 3β-methoxy-4aβ,5β-epoxide *IX* either. Hence, the through-space effect

of the methoxy group, which is evidently sufficiently distinct as to suppress the –I effect, is probably operative in the case of 4aα,5α-epoxide *VI* as well, where the conformation of the seven-membered ring permitting the through-space interaction of the free electron pair of the methoxy group and of the epoxide oxygen, could be conformation *F* (Fig. 2).

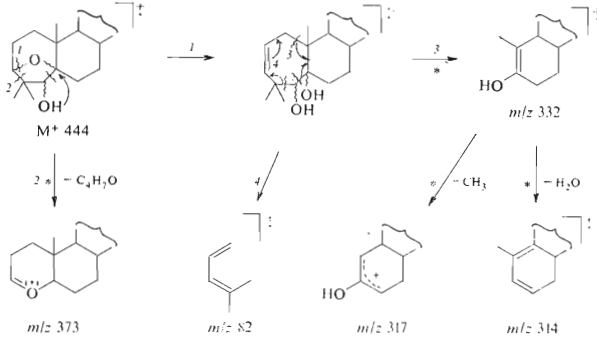



*E* *F*

FIG. 2

Conformations of the ring A of 4aβ,5β-epoxide *IX* and 4aα,5α-epoxide *VI*

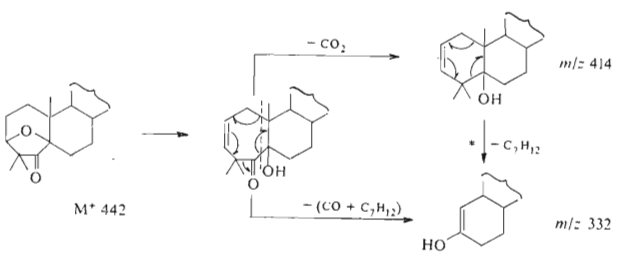
In connection with the study of the mass spectra of the products of reductive opening of epoxides *I*–*XII*, which will be published elsewhere, the mass spectra of cyclic epoxides *XIII*, *XVII*, *XXV* and *XXVIII* and of semiketal *XVIII* were also investigated. The mass spectra of both isomeric 4a-hydroxy 3,5-epoxides *XIII* and *XXV* are dominated by the ion *m/z* 332, which is formed on decomposition of the rearranged molecular ion (Scheme 1, paths *1*, *3*). If this cleavage takes place by RDA




SCHEME 1

mechanism the charge is transferred to the butadiene system of the ion $m/z$ 82 which possesses the best possibility for delocalization. The expulsion of the species $C_4H_7O$ represents a side-route of the decomposition of $M^+$, resulting in the formation of the oxonium ion $m/z$ 373. The ion $m/z$ 332 further decomposes only to a small extent, under formation of ions $m/z$ 317, $m/z$ 314 (Scheme 1) and $m/z$ 247 ($C_{18}H_{31}$). The mass spectra of both isomeric compounds *XIII* and *XXV* hardly differ from one another.

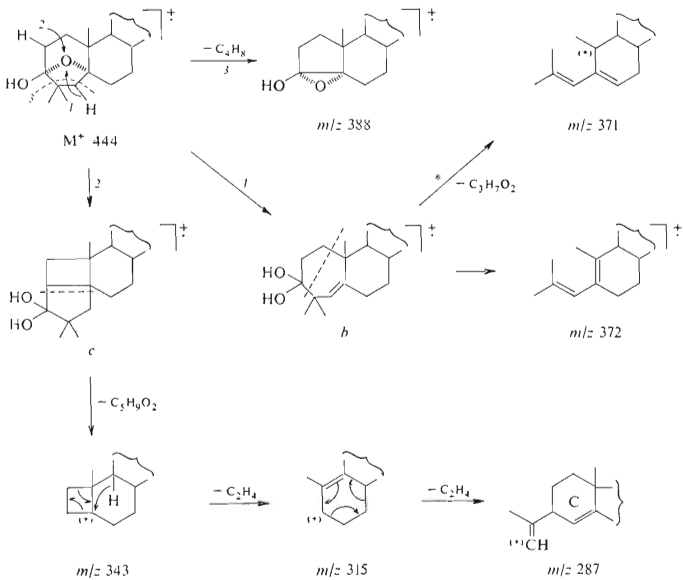
The mass spectra of 4a-ketones *XVII* and *XXVIII* are also dominated by ion $m/z$ 332 which is the sole important product of decomposition of their molecular ions. The very instable molecular ion is immediately rearranged to structure *a* (Scheme 2) which is stabilized by expulsion of a hydrogen atom, the radical $CH_3$ or the




SCHEME 2

molecule of CO. The last reaction leads to ion $m/z$ 414 which undergoes elimination of $C_7H_{12}$ under formation of ion $m/z$ 332 (the metastable transition $m/z$ 414→ → $m/z$ 332: $m^* = 266{\cdot}2$ was observed). It is probable that also concomitant loss of $C_7H_{12}$ and CO from the ion *a* takes place, resulting directly in the formation of ion $m/z$ 332. Its further fragmentation (loss of $CH_3$, $H_2O$ or $C_{18}H_{31}$) takes place to a small extent only. The mass spectra of both stereoisomeric 3,5-epoxides *XVII* and *XXVIII* can be distinguished by means of peaks $M^+$ and $[M-1]^+$: the first peak is twice as high as the second in the α-isomer, while in the β-isomer the situation is reversed. The formation of the characteristic ion $m/z$ 332 was also observed[15] during the fragmentation of cholestane-4a,5-diols and cholestan-5-ol-4a-one. This similarity is consistent with the assumption that the opening of the $C_{(3)}$—O bond represents the first step of the decomposition of $M^+$ of 3,5-epoxides *XIII*, *XXV*, *XVII* and *XXVIII*, under formation of the structure of 4a,5-diol (Scheme 1) or 5-ol-4a-one (Scheme 2). In comparison with the simple fragmentation of 4a-hydroxy derivatives *XIII* and *XXV* and 4a-ketones *XVII* and *XXVIII* the semi-ketal *XVIII* behaves under the

electron impact in a completely different way. While in the first case the fragmentation routes prevail, which begin with an easy cleavage of the $C_{(3)}$—O bond, in the case of the molecular ion of compound *XVIII* this bond is stable and $M^+$ undergoes fragmentation very reluctantly ($M^+$ forms the base peak). The main fragmentation route is initiated by the opening of the O-bridge on the opposite side, *i.e.* by the cleavage of the O—$C_{(5)}$ bond. The ion *b* formed (Scheme 3, path *1*) is cleaved in the




SCHEME 3

allylic position losing the particle $C_3H_7O_2$ (the process is acompanied by an intensive metastable transition: $m^* = 310{\cdot}0$) or $C_3H_6O$. The ions $m/z$ 371 and $m/z$ 372 are stabilized by the delocalization of the charge in the butadiene system and therefore they are not further fragmented. If a splitting off of a hydrogen atom from the $C_{(2)}$ atom takes place during the opening of the O-bridge, the ion *c* is formed (Scheme 3, path *2*) which splits off the species $C_5H_9O_2$ under formation of the ion $m/z$ 343. The ions $m/z$ 315 and $m/z$ 287, are products of gradual elimination of two molecules

$C_2H_4$ from the species $m/z$ 343. Another fragmentation route of the molecular ion consists in the initiation of the elimination of an isobutene molecule (Scheme 3, path *3*). The ion $m/z$ 388 formed in this way is rearranged and finally loses the particle $C_3H_3$ (the corresponding $m^* = 319{\cdot}9$ was observed) under formation of the ion $m/z$ 349. The mechanism of this process which must include a skeletal rearrangement is not clear. The ion $m/z$ 331 is formed by the loss of the side chain $C_8H_{17}$ from $M^+$.

TABLE III

Analytical and physical data of the products of reductive opening of epoxides *I*—*XII*

| Compound | Formula (m.w.) | Calculated/Found | | M.p., °C $[\alpha]_D^{20}$ |
|---|---|---|---|---|
| | | % C | % H | |
| *XIII* | $C_{30}H_{52}O_2$ (444·7) | 81·02<br>81·20 | 11·79<br>11·87 | 250—252<br>+39°[a] |
| *XIV* | $C_{30}H_{54}O_2$ (446·7) | 80·65<br>80·41 | 12·18<br>12·05 | 160—162<br>— 8° |
| *XVI* | $C_{31}H_{56}O_2$ (460·6) | 80·80<br>80·53 | 12·25<br>12·11 | 135—137<br>+11° |
| *XIX* | $C_{30}H_{54}O_2$ (446·7) | 80·65<br>80·24 | 12·18<br>11·77 | 230—232<br>—13° |
| *XX* | $C_{31}H_{56}O_2$ (460·76) | 80·80<br>80·76 | 12·25<br>12·38 | 115—117<br>—23° |
| *XXII* | $C_{30}H_{54}O_2$ (446·7) | 80·65<br>80·54 | 12·18<br>12·24 | 215—217<br>+91° |
| *XXIII* | $C_{31}H_{54}O_2$ (458·7) | 81·16<br>80·85 | 11·86<br>11·62 | 140—142<br>+11° |
| *XXIV* | $C_{31}H_{56}O_2$ (460·76) | 80·80<br>80·35 | 12·25<br>12·13 | 113—115<br>+57° |
| *XXV* | $C_{30}H_{52}O_2$ (444·7) | 81·02<br>80·62 | 11·79<br>11·46 | 248—25ℓ<br>+12° |
| *XXVI* | $C_{30}H_{54}O_2$ (446·7) | 80·65<br>80·41 | 12·18<br>12·08 | 145—147<br>+64° |
| *XXVII* | $C_{31}H_{54}O_2$ (458·7) | 81·16<br>80·99 | 11·86<br>11·68 | 130—132<br>—26° |
| *XXIX* | $C_{30}H_{52}O$ (428·7) | 84·04<br>83·96 | 12·23<br>12·11 | 131—133<br>+52° |

[a] Optical rotation was measured in pyridine.

## EXPERIMENTAL

The melting points were determined on a Kofler block and they are not corrected. Optical rotations, unless stated otherwise, were measured in chloroform. The infrared spectra were measured on a Zeiss UR 20 instrument in tetrachloromethane, unless otherwise stated, the $^1$H-NMR spectra, unless stated otherwise, were measured on a Tesla B 476 (60 MHz) instrument in deuteriochloroform, using tetramethylsilane as internal reference. The chemical shifts are given in ppm. The CD spectra were measured on a Dichrographe II apparatus (Jouan-Roussel) in dioxane. The mass spectra were measured on an AEI MS 902 (Associated Electric Industries, Manchester, Great Britain) mass spectrometer with double focussing. The exact values observed range within the $\pm 3$ ppm of the theoretical value. The identity of the samples prepared in various ways was checked by mixture melting point determination and infrared spectra measurements. The term "conventional work-up" means: the solution was washed with 5% hydrochloric acid, 5% aqueous potassium hydrogen carbonate, water, dried over sodium sulfate and the solvent was distilled in a vacuum. Preparative chromatography of crude reaction mixtures was carried out, unless stated otherwise, on silica gel plates 20 × 20 cm in light petroleum–ether 9 : 1. The required zones were combined, eluted with ether and the solvent was distilled off under reduced pressure.

### Reaction of Epoxides *I*—*XII* with Lithium Aluminum Hydride

Lithium aluminum hydride (100 to 400 mg) was added to a solution of epoxide (50 to 200 mg) in dioxane (5 to 10 ml) and the mixture was refluxed for 3 to 9 h. The excess of the hydride was decomposed with a saturated aqueous sodium sulfate solution and the mixture was filtered through a small column of sodium sulfate. The filtrate was concentrated in a vacuum and the residue was chromatographed on one to four silica gel plates in light petroleum–ether 8 : 2. The yields of the main products of reductive opening of the epoxide *I*—*XII* are given in Table I. The $^1$H-NMR data of the products are given in Table II and their analytical and physical data in Table III.

### 3β-Methoxy-4,4-dimethyl-4aα,5-epoxy-A-homo-5α-cholestane (*III*)

Potassium (100 mg) was added to a solution of epoxide *I*, ref.[3] (100 mg), in benzene (10 ml) and the mixture was heated under nitrogen to 40°C. Methyl iodide (2 ml) was then added and the mixture refluxed under nitrogen at 80°C for 2 h. After cooling to 0°C the excess of potassium was decomposed with methanol. The precipitate was filtered off and the filtrate washed with water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue (100 mg) was chromatographed on 2 silica gel plates. The corresponding zones were combined and eluted affording 80 mg of methoxy derivative *III* which was crystallized from methanol, m.p. 175—177°C, $[\alpha]_D^{20} = +61°$ (*c* 0·5). IR spectrum: 2 825, 1 100, 956, 925 cm$^{-1}$, $^1$H-NMR spectrum (Varian HA 100): 0·67 (s, 3 H, 18-$CH_3$); 0·86 (d, 6 H, 26 + 27-$CH_3$, $J = 6$ Hz); 0·89 (d, 3 H, 21-$CH_3$, $J = 6$ Hz); 0·975 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 1·06 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 1·23 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 2·36 (s, 1 H, $C_{(4a)}$—H); 2·75 (dd, 1 H, $C_{(3)}$—H, $J = 3 + 10$ Hz); 3·29 (s, 3 H, O—$CH_3$). For $C_{31}H_{54}O_2$ (458·7) calculated: 81·16% C, 11·86% H; found: 80·24% C, 12·32% H.

### 3α-Methoxy-4,4-dimethyl-4aα,5-epoxy-A-homo-5α-cholestane (*VI*)

Potassium (100 mg) was added to a solution of epoxide *IV*, ref.[3], (80 mg) in benzene (8 ml) and the mixture was heated to 40 °C under nitrogen. Methyl iodide (3 ml) was added and the mixture was heated at 80°C under nitrogen for 5 h. The working up as in the preparation of compound *III*

gave 80 mg of a crude product which was chromatographed on 2 silica gel plates. The combined corresponding zones were worked up affording 60 mg of methoxy derivative *VI* which was crystallized from methanol (48 mg), m.p. 128–130°C, $[\alpha]_D^{20} = +13°$ (*c* 0·5). IR spectrum: 2 825, 1 110, 1 094, 961 $cm^{-1}$. $^1$H-NMR spectrum (Varian HA 100); 0·61 (s, 3 H, 18-$CH_3$); 0·79 (d, 6 H, 26+27-$CH_3$, $J = 6$ Hz); 0·83 (d, 3 H, 21-$CH_3$, $J = 6$ Hz); 0·97 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 1·02 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 1·17 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 2·27 (d, 1 H, $C_{(4a)}$—H, $J = 2$ Hz); 2·82 (mt, 1 H, $C_{(3)}$—H); 3·20 (s, 3 H, O—$CH_3$); for $C_{31}H_{54}O_2$ (458·7) calculated: 81·16% C, 11·86% H; found: 81·14% C, 11·83% H.

3β-Methoxy-4,4-dimethyl-4aβ,5-epoxy-A-homo-5β-cholestane (*IX*)

Potassium (130 mg) was added to a solution of *VII*, ref.[3] (130 mg), in benzene (13 ml) and the mixture was heated to 40°C under nitrogen. Methyl iodide (2·7 ml) was then added and the mixture was refluxed under nitrogen at 80°C for 2 h. Working up as in the preceding cases gave 130 mg of a crude product which was chromatographed on 2 silica gel plates. The combined corresponding zones were worked up affording 90·4 mg of derivative *IX* which was crystallized from methanol (75 mg), m.p. 109–111°C, $[\alpha]_D^{20} = +37°$ (*c* 0·5). IR spectrum: 2 825, 1 107, 962, 959 $cm^{-1}$. $^1$H-NMR spectrum (Varian HA 100); 0·64 (s, 3 H, 18-$CH_3$); 0·82 (d, 6 H, 26+27-$CH_3$, $J = 6$ Hz); 0·86 (d, 3 H, 21-$CH_3$, $J = 6$ Hz); 1·00 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 1·04 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 1·19 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 2·325 (d, 1 H, $C_{(4a)}$—H, $J = 1·5$ Hz); 2·855 (mt, 1 H, $C_{(3)}$—H); 3·195 (s, 3 H, O—$CH_3$). For $C_{31}H_{54}O_2$ (458·7) calculated: 81·16% C, 11·86% H; found: 81·09% C, 11·72% H.

3α-Methoxy-4,4-dimethyl-4aβ,5-epoxy-A-homo-5β-cholestane (*XII*)

Potassium (80 mg) was added to a solution of epoxide *X*, ref.[3] (90 mg), in benzene (9 ml) and the mixture was heated at 40°C under nitrogen. Methyl iodide (2 ml) was added and the mixture heated under nitrogen at 80°C for 2 h. The same working up procedures as in the preceding cases gave 90 mg of a crude product which was chromatographed on 2 silica gel plates. The combined corresponding zones were eluted, affording 81 mg of methoxy derivative *XII* which was crystallized from methanol (66 mg), m.p. 108–109°C, $[\alpha]_D^{20} = -4°$ (*c* 0·5). IR spectrum: 2 825, 1 101, 962, 959 $cm^{-1}$. $^1$H-NMR spectrum: 0·66 (s, 3 H, 18-$CH_3$); 0·86 (d, 6 H, 26+27-$CH_3$, $J = 6$ Hz); 0·89 (d, 3 H, 21-$CH_3$, $J = 6$ Hz); 1·025 (s, 6 H, 19-$CH_3$ + $C_{(4)}$—$CH_3$ of $C_{(4)}$—$CH_3$ + + $C_{(4)}$—$CH_3$); 1·225 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 2·375 (s, 1 H, $C_{(4a)}$—H); 2·75 (mt, 1 H, $C_{(3)}$—H); 3·29 (s, 3 H, O—$CH_3$). For $C_{31}H_{54}O_2$ (458·7) calculated: 81·16% C, 11·86% H; found: 81·01% C, 11·56% H.

3β-Acetoxy-4,4-dimethyl-A-homo-5α-cholestan-5-ol (*XV*)

Diol *XIV* (30 mg) was acetylated with acetic anhydride (0·1 ml) in pyridine (2 ml) overnight. The conventional working up procedure gave 30 mg of a crude product which was crystallized from methanol, giving 16 mg of acetoxy derivative *XV*, m.p. 139–141°C, $[\alpha]_D^{20} = +2°$ (*c* 0·5). IR spectrum: 3 630, 1 731, 1 255, 1 022 $cm^{-1}$. For $C_{32}H_{46}O_3$ (488·8) calculated: 78·63% C, 11·55% H; found: 78·18% C, 11·46% H.

4,4-Dimethyl-3a,5-epoxy-A-homo-5α-cholestan-3β-ol (*XVIII*)

*a*) Chromium trioxide (25 mg) was added to a solution of diol *XIV* (30 mg) in pyridine (2 ml) and the mixture was allowed to stand at room temperature overnight. The conventional work-up

gave 30 mg of a crude product which was chromatographed on a silica gel plate in light petroleum–ether (95·5). The required zone gave 22 mg of semiketal *XVIII*, which was crystallized from methanol (15 mg), m.p. 119–121°C, $[\alpha]_D^{20} = +2°$ (*c* 0·5). IR spectrum: 1 202, 3 620 $cm^{-1}$. $^1$H-NMR spectrum: 0·63 (s, 3 H, 18-$CH_3$); 0·72 (s, 3 H, 19-$CH_3$ or $C_{(4)}$—$CH_3$); 0·85 (d, 9 H, 21 + 26 + 27-$CH_3$, $J = 6$ Hz); 1·03 (s, 6 H, 19-$CH_3$ + $C_{(4)}$—$CH_3$ or $C_{(4)}$—$CH_3$ + $C_{(4)}$—$CH_3$) For $C_{30}H_{52}O_2$ (444·7) calculated: 81·02% C, 11·79% H; found: 80·89% C, 11·38% H.

*b*) Chromium trioxide (20 mg) was added to a solution of diol *XIX* (25 mg) in pyridine (2 ml) and the mixture was allowed to stand at room temperature overnight. The conventional work-up gave 25 mg of a crude product which was chromatographed on one silica gel plate in light petroleum–ether (95 : 5). The required zone was worked up affording 20 mg of semiketal *XVIII* which was crystallized from methanol (14 mg), m.p. 119–121°C, $[\alpha]_D^{20} = +2°$ (*c* 0·5).

4,4-Dimethyl-3β,5-epoxy-A-homo-5β-cholestan-4a-one (*XVII*)

Chromium trioxide (30 mg) was added to a solution of alcohol *XIII* (30 mg) in pyridine (3 ml) and the mixture was allowed to stand at room temperature overnight. The conventional work-up gave 30 mg of a crude product which was submitted to preparative thin-layer chromatography on one silica gel plate in light petroleum–ether (95 : 5). The required zone was worked up affording 25 mg of ketone *XVII* which was crystallized from methanol (12 mg), m.p. 102–104°C, $[\alpha]_D^{20} = +40°$ (*c* 0·5, dioxane). IR spectrum: 1 747, 1 054, 1 029 $cm^{-1}$. CD spectrum: $\Delta\varepsilon_{304} = +0·89$. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·21% C, 10·83% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestan-4a-one (*XXVIII*)

Chromium trioxide (20 mg) was added to a solution of alcohol *XXV* (25 mg) in pyridine (2 ml) and the mixture was allowed to stand at room temperature overnight. The conventional work-up gave 25 mg of a crude product which was chromatographed on one silica gel plate in light petroleum–ether (95 : 5). The required zone was worked up affording 20 mg of ketone *XXVIII* which was crystallized from methanol (14 mg), m.p. 120–121°C, $[\alpha]_D^{20} = -60°$ (*c* 0·5). IR spectrum: 1 750, 1 010, 951 $cm^{-1}$. CD spectrum: $\Delta\varepsilon_{290} = -3·58$. For $C_{30}H_{50}O_2$ (442·7) calculated: 81·39% C, 11·38% H; found: 81·06% C, 11·09% H.

Reduction of Ketone *XVII* with Lithium Aluminum Hydride

An excess of lithium aluminum hydride was added to a solution of ketone *XVII* (35 mg) in ether (3 ml) and the mixture was allowed to stand at room temperature for 15 min. The excess of hydride was decomposed with a saturated aqueous solution of sodium sulfate and the mixture was filtered through a small column of sodium sulfate. The filtrate was concentrated in a vacuum and the residue (35 mg) crystallized from methanol giving 20 mg of alcohol *XIII*, m.p. 250 to 252°C, $[\alpha]_D^{20} = +39°$ (*c* 0·5, pyridine).

Methylation of Diols *XIV*, *XIX* and *XXII*

Potassium (40 mg) was added to a solution of diol (40 mg) in benzene (4 ml) and the mixture was heated to 40°C under nitrogen. Methyl iodide (1 ml) was then added and the mixture was heated at 80°C under nitrogen for 1 h. After cooling to 0°C the excess of potassium was decomposed with methanol. The precipitate was filtered off and the filtrate washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The crude product was chromatographed

on a silica gel plate. The required zone was worked up to give 3-methoxy derivatives *XVI*, *XX* or *XXIV*, respectively, the analytical data of which are presented in Table III.

Mass Spectra

The mass spectra were measured on the double focussing AEI MS 902 (Associated Electric Industries, Manchester, Great Britain) spectrometer. The samples were introduced by direct inlet into the ion source heated at 140—170°C. The low-resolution mass spectra were recorded at a 1 000 m.u. resolving power and 70 eV. The high-resolution spectra were measured using the $m_1/(m_1 - m_2) = 10\,000$ resolving power (definition of the 10% valley). The exact masses determined were within the theoretical value of $\pm 3$ ppm. Partial mass spectra (most important peaks from the upper part of the spectra) of compounds *XIII*, *XVII*, *XVIII*, *XXV* and *XXVIII* are presented. The masses and the relative abundances (in brackets) in percents of the base peak are also given. The elemental composition, corresponding to the exact accurate value found (if determined), follows the relative abundance in brackets.

*XIII*: 82 (88, $C_6H_{10}$); 201 (13, $C_{15}H_{21}$); 206 (6); 219 (9, $C_{15}H_{23}O$); 247 (4·5); 314 (8); 317 (12); 332 (100, $C_{23}H_{40}O$); 355 (4); 356 (3·3); 357 (3·6); 373 (8·5, $C_{26}H_{45}O$); 426 (4·5); $M^+$ 444 (7·2, $C_{30}H_{52}O_2$).

*XVII*: 201 (6·3, $C_{15}H_{21}$); 206 (3); 219 (4·7, $C_{15}H_{23}O$); 247 (2); 274 (8); 299 (1); 314 (4·2); 317 (6·3); 332 (100, $C_{23}H_{40}O$); 414 (3, $C_{29}H_{50}O$); 427 (0·7); $M^+$ 442 (0·5, $C_{30}H_{50}O_2$).

*XVIII*: 275 (7·7); 287 (9·2, $C_{21}H_{35}$); 315 (8·1, $C_{23}H_{39}$); 331 (17·7, $C_{22}H_{35}O_2$); 343 (14, $C_{25}H_{43}$); 349 (14·4, $C_{23}H_{41}O_2$); 371 (39, $C_{27}H_{47}$); 388 (24·4, $C_{26}H_{44}O_2$); 401 (4); 411 (3); 429 (3·3); $M^+$ 444 (100, $C_{30}H_{52}O_2$).

*XXV*: 82 (54, $C_6H_{10}$); 201 (2·3, $C_{15}H_{21}$); 219 (2·4, $C_{15}H_{23}O$); 247 (1·8, $C_{18}H_{31}$); 314 (2·1); 317 (6·3); 332 (100, $C_{23}H_{40}O$); 355 (2·8); 356 (2·8); 359 (2·7); 373 (8·3, $C_{26}H_{45}O$); 398 (1·6, $C_{29}H_{50}$); 426 (4·7); $M^+$ 444 (10·5, $C_{30}H_{52}O_2$).

*XXVIII*: 201 (4, $C_{15}H_{21}$); 206 (1·3), 219 (2·7, $C_{15}H_{23}O$); 247 (1·2); 274 (1·2); 299 (0·8); 314 (2·5, $C_{23}H_{28}$); 317 (5·3, $C_{22}H_{37}O$); 332 (100, $C_{23}H_{40}O$); 414 (1·3, $C_{29}H_{50}O$); 427 (0·6); $[M-1]^+$: 441 (0·14); $M^+$ 442 (0·07).

*The analyses were carried out in the Analytical laboratory of this Institute under the direction of Dr J. Horáček. We thank Mrs K. Matoušková for the measurement of the infrared spectra and Dr J. Smolíková for their interpretation. We also thank Mrs J. Jelínková for the measurement of the* $^1$H NMR *spectra, and Mrs M. Bárová for technical assistance.*

REFERENCES

1. Velgová H., Trka A.: This Journal, in press.
2. Parker R. E., Isaack N. S.: Chem. Rev. *59*, 737 (1959).
3. Velgová H., Trka A.: This Journal, in press.
4. Itô S., Endo K., Ogino T., Takeuchi H., Watanabe T.: Tetrahedron Lett. *1967*, 2581.
5. Velgová H.: This Journal, in press.
6. Eliel E. L.: *Steric Effects in Organic Chemistry* (M. S. Newman, Ed.), p. 130. Wiley, New York 1956.
7. Jones J. G. Ll., Marples B. A.: J. Chem. Soc., Perkin 1, *1972*, 792.
8. Chrétien-Bessière Y., Desalbres H., Monthéard J.-P.: Bull. Soc. Chim. Fr. *1963*, 2546.
9. Kočovský P., Černý V., Synáčková M.: This Journal *44*, 1483 (1979).

10. Rickborn B., Lamke W. E.: J. Org. Chem. *32*, 537 (1967).
11. Pierre J. L., Handel H., Perraud R.: Tetrahedron *31*, 2795 (1975).
12. Hoffmann R.: Accounts Chem. Res. *4*, 1 (1971).
13. Paddon-Row M. N., Patney H. K., Warrener R. N.: J. Chem. Soc. Chem. Commun. *1978*, 296.
14. Paddon-Row M. N., Patney H. K., Warrener R. N.: J. Org. Chem. *44*, 3908 (1979).
15. Wyllie S. G.: Org. Mass. Spectrom. *6*, 559 (1972).

Translated by Ž. Procházka.