ACID CATALYSED OPENING OF 4,4-DIMETHYL-4a,5-EPOXY-A-HOMOCHOLESTANE DERIVATIVES*

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The acid catalysed cleavage of 4,4-dimethyl-4a,5-epoxy-A-homocholestane derivatives bearing an oxygen-containing substituent (OH, $OCOCH_3$, OCH_3) in the position 3 with hydrobromic acid or aqueous perchloric acid was investigated. It was found that 4a,5-epoxides of 4,4-dimethyl--A-homocholestane series are opened on the side of the more substituted carbon atom $C_{(5)}$, where a normal cleavage leads to the formation of 4a-hydroxy-5,6-unsaturated derivatives, while the participation of the substituent in the position 3 leads to 3,5-epoxides. In none of the investigated epoxides was an attack of an external nucleophile observed. The effect of the nature of the substituent in the position 3 on the ratio of the products of a normal cleavage and the participation of the 3-substituent is discussed from the point of view of conformational effects. The dependence of the products ratio on the nucleophilicity of the acid used is also discussed.

In our preceding paper[1] we investigated the stereochemistry of the reductive opening of the epoxide ring of 4,4-dimethyl-4a,5-epoxy-A-homocholestane derivatives carrying an oxygen-containing substituent in the position 3 (*i.e.* OH, $OCOCH_3$, OCH_3). We observed that a suitably oriented substituent in the position 3 may participate in the reductive opening of the 4a,5-epoxide ring under formation of 3,5-epoxides. Recently the question of the participation of the oxygen-containing substituent (OH, $OCOCH_3$, OCH_3) in the acid catalysed opening of some epoxides of cholestane and B-homocholestane series[2-5] was investigated in our laboratory in greater detail. It was found that the hydroxyl group and the methoxyl group participate in the acid catalysed opening of the epoxide ring through the $(O)^n$ process, while the acetoxy groups can participate either through the $(O)^n$ or the $(O)^{\pi,n}$ process, the $6(O)^{\pi,n}$ participation being preferred to the $5(O)^n$ participation (for the notation see ref.[6]). It was also found that under the effect of a strong acid representing the type of a strong nucleophile (as for example in the case of hydrobromic acid), an external attack is preferred if compared with the effect of a strong acid representing the type of a weak nucleophile (as for example aqueous perchloric acid). Hence, it was interesting to find out whether and in what way the oxygen-containing substituent in the position 3 would participate in the acid catalysed cleavage of 4a,5-epoxides of 4,4-dimethyl-

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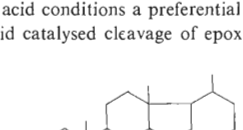
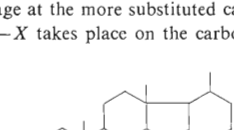
-A-homocholestane series and whether this process would be accompanied by a competitive attack of the external nucleophile. The acid catalysed opening of epoxides *I*–*X*, the preparation of which has been described earlier (epoxides *I*–*VIII*, ref.[7], epoxides *IX*, *X* ref.[1]), was carried out both with hydrobromic acid in chloroform and with aqueous perchloric acid in acetone (epoxides *I*–*IV*, *VI*, *VIII*–*X*) or dioxane (epoxides *V* and *VII*, since they were poorly soluble in acetone). The yields of the main products of cleavage of epoxides *I*–*X* are shown in Table I.

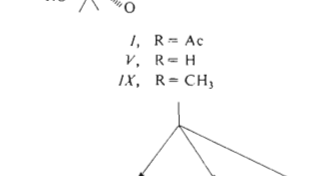
In agreement with the observed tendency of trisubstituted epoxides to undergo under acid conditions a preferential cleavage at the more substituted carbon atom[8], the acid catalysed cleavage of epoxides *I*–*X* takes place on the carbon atom $C_{(5)}$



I, R = Ac
V, R = H
IX, R = CH_3

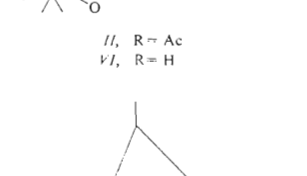


II, R = Ac
VI, R = H



XIII, R^1 = Ac, R^2 = H
XIV, R^1 = R^2 = H

XV

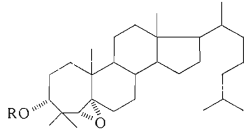


XI, R = Ac
XII, R = H

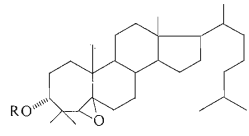
XVI, R^1 = Ac, R^2 = H
XVII, R^1 = R^2 = H

exclusively, where the normal cleavage leads to the formation of 4a-hydroxy-5,6-unsaturated derivatives, while the participation of the substituent in the position 3 leads to the formation of 3,5-epoxides. The structures of the allylic alcohols and the 3,5-epoxides formed (Table I) have been described earlier[1,9]. None of the investigated epoxides *I*–*X* gave either with aqueous perchloric acid or hydrobromic acid the products corresponding to an attack of the external nucleophile in any appreciable amount *i.e.* 4a,5-diols or bromohydrins. The nature of the acid used however influenced the reactivity of the 4a,5-epoxide rings in compounds in which the participation of the substituent in the position 3 does not play a role, and also the ratio of the

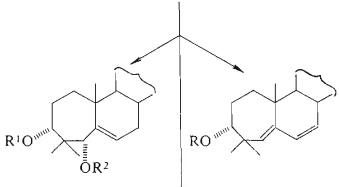
products of a normal cleavage and the participation of the 3-substituent in the case of epoxides in which a participation takes place. In the case of epoxides *I–IV*, *VI* and *VII* a substantial difference in reactivity of the 4a,5-epoxide ring was observed in α- and β-epoxides when aqueous perchloric acid was used. While 4aβ,5β-epoxides *II*, *IV* and *VI* are opened with aqueous perchloric acid relatively easily under formation of corresponding allylic alcohols, the 4aα,5α-epoxides *I*, *III* and *VII* are practically stable under the same reaction conditions and the corresponding allylic alcohols are formed in small amounts only (Table I). When hydrobromic acid was used the difference in the reactivity of the epoxide ring in epoxides *I–IV*, *VI* and *VII* was practically hardly observable, and both α- and β-epoxides afforded corresponding allylic alcohols as the main product of cleavage (Table I). However, under the given



III, R = Ac
VII, R = H

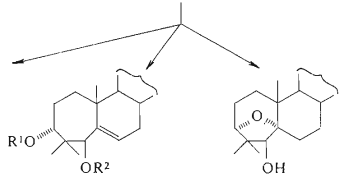


IV, R = Ac
VIII, R = H
X, R = CH_3



XXI, R^1 = Ac, R^2 = H
XXII, R^1 = R^2 = H

XVIII, R = Ac
XIX, R = H
XX, R = CH_3



XXV, R^1 = Ac, R^2 = H
XXVI, R^1 = R^2 = H
XXVII, R^1 = CH_3, R^2 = H

XXVIII

XXIII *XXIV*

reaction conditions these primarily formed allylic alcohols undergo a subsequent acid-catalysed elimination reaction, leading to the formation of 4a,6-dienes *XI*, *XII*, *XVIII* and *XIX* in the ^{1}H NMR spectra of which the signals of three olefinic protons are detectable in agreement with the proposed structure (Table II). Under the given conditions 3α-hydroxy-4a,6-diene *XIX* further undergoes an acid-catalysed intramolecular cyclisation reaction which leads to the formation of 3,5-epoxide *XXIII*. In the ^{1}H NMR spectrum of 3,5-epoxide *XXIII* the signals of one CH—O proton and of two olefinic protons are observed in agreement with the proposed structure

TABLE I

Yields of the main products (% of the total yield) of the cleavage of epoxides *I*—*X*

Starting epoxide	Reagent	Starting epoxide	Allylic alcohol	4a,6-Diene	Other products	Total yield, %
I	HBr	4 (*I*)	85 (*XIII*)[a]	11 (*XI*)	—	97
	$HClO_4/H_2O$	90 (*I*)	10 (*XIII*)[a]	—	—	100
II	HBr	8 (*II*)	89 (*XVI*)[a]	3 (*XI*)	—	100
	$HClO_4/H_2O$	22 (*II*)	78 (*XVI*)[a]	—	—	100
III	HBr	12 (*III*)	83 (*XXI*)[a]	3 (*XVIII*)	—	100
	$HClO_4/H_2O$	98 (*III*)	2 (*XXI*)[a]	—	—	86
IV	HBr	8 (*IV*)	77 (*XXV*)[a]	15 (*XVIII*)	—	86
	$HClO_4/H_2O$	28 (*IV*)	72 (*XXV*)[a]	—	—	98
V	HBr	—	9 (*XIV*)[a]	—	91 (*XV*)[b]	98
	$HClO_4/H_2O$	—	—	—	100 (*XV*)[b]	96
VI	HBr	—	91 (*XVII*)[a]	9 (*XII*)	—	93
	$HClO_4/H_2O$	15 (*VI*)	85 (*XVII*)[a]	—	—	91
VII	HBr	—	15 (*XXII*)[a]	62 (*XIX*)	23 (*XXIII*)	83
	$HClO_4/H_2O$	84 (*VII*)	16 (*XXII*)[a]	—	—	91
VIII	HBr	—	20 (*XXVI*)[a]	—	80 (*XXVIII*)[b]	90
	$HClO_4/H_2O$	—	15 (*XXVI*)[a]	—	85 (*XXVIII*)[b]	93
IX	HBr	—	—	—	100 (*XV*)[b]	96
	$HClO_4/H_2O$	—	—	—	100 (*XV*)[b]	96
X	HBr	—	76 (*XXVII*)[b]	16 (*XX*)	8 (*XXVIII*)[b]	86
	$HClO_4/H_2O$	—	96 (*XXVII*)[b]	—	4 (*XXVIII*)[b]	92

[a] The analytical and the physical data of the substances were identical with the data from literature[9]. [b] The analytical and the physical data of the substances were identical with the data from literature[1].

(Table II). On hydrogenation on Adams catalyst the unsaturated 3,5-epoxide *XXIII* afforded the corresponding saturated analogue *XXIV*.

3β-Substituted 4aα,5α-epoxides *I*, *V* and *IX* and 3α-substituted 4aβ,5β-epoxides *IV*, *VIII* and *X* represent a type of compound in which the participation of the substituent in the position 3 might be operative during the acid-catalysed opening of the epoxide ring. Contrary to our expectation that both acetoxy, hydroxy and methoxy groups in the position 3 would participate in the cleavage of the 4a,5-epoxide ring of the above mentioned epoxides *I*, *IV*, *V*, *VIII*–*X*, it was found that the acetoxy group in position 3 (epoxides *I* and *IV*) does not participate and that epoxides *I* and *IV* afford merely the product of normal cleavage (*i.e.* allylic alcohols *XIII* and *XXV*, and 4a,6-dienes *XI* and *XVIII*, respectively, see Table I) when hydrobromic or aqueous perchloric acids are used. A study of Dreiding models has shown that for the participation of the substituent in the position 3 the most favourable conformations of the seven-membered ring A of the 4aα,5α and 4aβ,5β-epoxides of the 4,4-dimethyl-A-homocholestane series are the conformations *A* and *B* (Fig. 1) in which the sub-

TABLE II

^{1}H NMR data of the products of the cleavage of epoxides *I*–*X*. The ^{1}H NMR spectra were measured in deuteriochloroform using tetramethylsilane as internal reference. The chemical shifts are given in ppm, δ-scale, the coupling constants *J* and the halfwidths $W_{1/2}$ in Hz. The following abbreviations were used for the characterization of the signals; s singlet, d doublet, bd broad doublet, dd doublet of a doublet, mt multiplet.

Compound	$C_{(3)}$—H	$C_{(4a)}$—H	$C_{(6)}$—H	$C_{(7)}$—H
XI[a]	4·61 (dd) $J = 11·2 + 2$	5·09 (s)	5·53 (d, $J_{6,7} = 10·4$)	5·81 (dd, $J_{7,8} = 1·6$, $J_{7,6} = 10·4$)
XII[b]	3·425 (mt)	5·10 (s)	5·48 (d, $J_{6,7} = 10$)	5·81 (dd, $J_{7,8} = 2$, $J_{7,6} = 10$)
XVIII[a]	4·96 (mt) $J = 8 + 4·4$	5·09 (s)	5·54 (d, $J_{6,7} = 10$)	5·82 (dd, $J_{7,8} = 1·6$, $J_{7,6} = 10$)
XIX[b]	3·65 (mt)	5·075 (s)	5·51 (d, $J_{6,7} = 10$)	5·84 (dd, $J_{7,8} = 2$, $J_{7,6} = 10$)
XX[b]	3·09 (mt)	5·09 (s)	5·46 (d, $J_{6,7} = 10$)	5·82 (dd, $J_{7,8} = 2$, $J_{7,6} = 10$)
XXIII[b]	3·55 (bd) $W_{1/2} = 8$	—	5·71 (dd, $J_{6,7} = 10$, $J_{6,8} = 2$)	5·47 (dd, $J_{7,8} = 2·8$, $J_{7,6} = 10$)

[a] The spectra were measured on a Varian XL 200 instrument. [b] The spectra were measured on a Tesla B 476 (60 MHz) instrument.

stituent in 3 assumes a quasiaxial conformation while its distance from the reaction centre, *i.e.* from the carbon atom $C_{(5)}$, is in both conformations, *A* and *B*, about 0·31 – 0·32 nm. The fact that in the case of 3-acetoxy epoxides *I* and *IV* the formation of 3,5-epoxides as products of a 5(O)^n participation or any other participation products was not observed, is probably a result of conformational effects, *i.e.* that the relatively bulky acetoxy group assumes preferentially a quasiequatorial conformation, for example in the *C* and *D* conformations of the seven-membered ring A (Fig. 1), which do not enable the effect of participation. A further effect which goes in the same direction is also the decrease of the electron density on the ethereal oxygen of the acetoxy group under the effect of the carbonyl group.

3β-Hydroxy-4aα,5α-epoxide *V* and 3α-hydroxy-4aβ,5β-epoxide *VIII* afford 3,5-epoxides *XV* and *XXVIII* as the main products of a cleavage with both hydrobromic and aqueous perchloric acid, in addition to a small amount of the products of normal cleavage, *i.e.* of allylic alcohols *XIV* and *XXVI*. When aqueous perchloric acid was used, the proportion of allylic alcohols was lower (Table I). For the formation of 3,5-epoxides *XV* and *XXVIII* the acid catalysed intramolecular cyclization of the primarily formed allylic alcohols *XIV* and *XXVI* might come into consideration in addition to the 5(O)^n participation of the 3-hydroxy group. However, this alter-

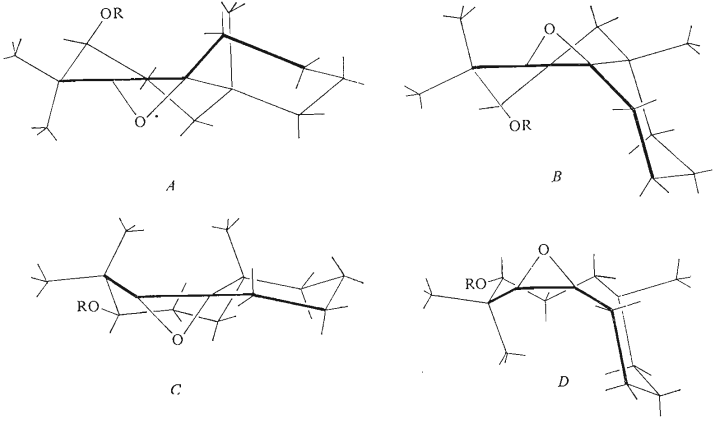


FIG. 1

Conformations of the ring A of 4aα,5α-epoxides *I*, *V* and *IX* and of 4aβ,5β-epoxides *IV*, *VIII* and *X*

native route may be eliminated as a possible route for the formation of 3,5-epoxides *XV* and *XXVIII* because alcohols *XIV* and *XXVI* remain practically unchanged in the reaction with aqueous perchloric acid. Hence, these epoxides are the products of a $5(O)^n$ participation of the 3-hydroxy group. 3,5-Epoxide *XV*, as a product of $5(O)^n$ participation of the methoxy group, is also the main product of the cleavage of 3β-methoxy-4aα,5α-epoxide *IX* both with hydrobromic acid and aqueous perchloric acid (Table I). However in the case of 3α-methoxy-4aβ,5β-epoxide *X* the product of a $5(O)^n$ participation of the methoxy group, *i.e.* the 3,5-epoxide *XXVIII*, is formed both with hydrobromic and aqueous perchloric acid in a very low yield and the main product of cleavage of the epoxide ring is the product of a normal cleavage, *i.e.* the allylic alcohol *XXVII* (Table I). The difference in the behaviour of 3β-substituted 4aα,5α-epoxides *V* and *IX* and 3α-substituted 4aβ,5β-epoxides *VIII* and *X*, *i.e.* the higher proportion of the products of a normal cleavage in the case of 3α-substituted 4aβ,5β-epoxides *VIII* and *X*, is probably the result of conformational effects, *i.e.* of the fact that the proportion of the conformers with a quasiequatorial 3-substituent in the equilibrium mixture of the conformers is higher in the case of 3α-substituted 4aβ,5β-epoxides *VIII* and *X* than in the case of 3β-substituted 4aα,5α-epoxides *V* and *IX*. This hypothesis is also supported by a study of Dreiding models which showed that the most favourable conformations of the seven-membered ring A, in which the 3-substituent assumes a quasiequatorial conformation, are the conformation *C* in the case of 4aα,5α-epoxides and the conformation *D* in the case of 4aβ,5β-epoxides. However, the conformation *C* seems less favourable owing to non-bonding interactions betwren $C_{(4\beta)}$- and 19-methyls than the conformation *D* and therefore it may be assumed that the proportion of the conformer *D* in the equilibrium mixture of the conformers of 4aβ,5β-epoxides *VIII* and *X* will be higher than the proportion of the conformer *C* in the equilibrium mixture of the conformers of 4aα,4α-epoxides *V* and *IX*. The weak increase in the ratio of the products of the normal cleavage and the $5(O)^n$ participation when hydrobromic acid was used for epoxides *V* and *VIII* corresponds to earlier observations[2-5] that in epoxides of cholestane series a strong nucleophile (bromide anion) attacks preferentially externally the epoxide ring under predominating or exclusive formation of products of normal diaxial cleavage.

EXPERIMENTAL

The melting points were determined on a Kofler melting point instrument and they are not corrected. Optical rotations were measured in chloroform. The infrared spectra were measured on a Zeiss UR 20 spectrophotometer in tetrachloromethane, unless stated otherwise. The ^1H NMR spectra were measured, unless otherwise stated, on a Tesla B 476 (60 MHz) instrument, in deuteriochloroform, using tetramethylsilane as internal reference. The chemical shifts are given in ppm. The identity of the samples prepared in various ways was checked by mixture melting point determinations and infrared spectra. The term "conventional work-up" means:

the solution was washed with 5% hydrochloric acid, a 5% aqueous potassium hydrogen carbonate solution and water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The crude products were chromatographed preparatively on silica gel thin-layer plates (20 × × 20 cm) in light petroleum–ether 9 : 1, unless stated otherwise. The required zones were combined, eluted with ether and the solvent evaporated in a vacuum.

Reaction of Hydrobromic Acid with Epoxides *I*—*X*

Hydrobromic acid (0·4 ml, 48%) was added to a solution of epoxide (100 mg) in chloroform (8 ml) and the mixture was shaken for 45 min, then poured into water and the product extracted with ether. The extract was washed with a 5% aqueous solution of potassium hydrogen carbonate and water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue was submitted to preparative thin-layer chromatography on 2 silica gel plates in light petroleum–ether (95 : 5). The yields of the products are given in Table I and their ^{1}H NMR spectra, analytical data and physical constants are presented in Tables II and III.

Reaction of Perchloric Acid with Epoxides *I*—*X*

Water (0·3 ml) and perchloric acid (0·12 ml, 72%) was added to a solution of epoxide (90 mg) in acetone (6 ml) and the mixture was allowed to stand at room temperature for 3 h. After pouring into water the product was extracted with ether. The extract was washed with a 5% aqueous solution of potassium hydrogen carbonate and water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue was submitted to preparative chromatography on 2 silica gel thin-layer plates as above. The yields of the products are given in Table I.

TABLE III

Analytical and physical data of the cleavage products of epoxides

Compound	Formula (m.w.)	Calculated/Found		M.p., °C $[\alpha]_D^{20}$
		%C	% H	
XI	$C_{32}H_{52}O_2$	81·99	11·18	111—113
	(468·7)	81·82	11·10	— 1°
XVIII	$C_{32}H_{52}O_2$	81·99	11·18	151—153
	(468·7)	81·22	11·20	—32°
XX	$C_{31}H_{52}O$	84·48	11·89	95—97
	(440·7)	84·30	11·71	—34°
XXIII	$C_{30}H_{50}O$	84·44	11·81	141—142
	(426·7)	83·93	11·54	—59°

4,4-Dimethyl-A-homo-4a,6-cholestadien-3β-ol (*XII*)

An excess of lithium aluminum hydride was added to a solution of acetoxy derivative *XI* (100 mg) in ether (5 ml) and the mixture was allowed to react at room temperature for 10 min. The excess of the hydride was decomposed with a saturated sodium sulfate solution in water and the mixture filtered through a small column of sodium sulfate. The filtrate was concentrated in a vacuum and the crude product (100 mg) was chromatographed preparatively on 2 silica gel plates in light petroleum–ether 8 : 2. The residue (90 mg) of the eluted combined corresponding zones was crystallized from methanol giving 56 mg of alcohol *XII*, m.p. 143–145°C, $[\alpha]_D^{20} = -59°$ (*c* 0·5). IR spectrum (chloroform): 3 625, 1 031, 1 018, 1 635, 1 605 cm^{-1}. For $C_{30}H_{50}O$ (426·7) calculated: 84·44% C, 11·81% H; found: 84·09% C, 11·71% H.

4,4-Dimethyl-A-homo-4a,6-cholestadiene-3α-ol (*XIX*)

An excess of lithium aluminum hydride was added to a solution of acetoxy derivative *XVIII* (100 mg) in ether (5 ml) and the mixture was allowed to stand at room temperature for 15 min. Using the same work-up procedure as in the case of the preparation of alcohol *XII* we obtained 100 mg of a crude product which was chromatographed preparatively on 2 silica gel plates in light petroleum–ether (8 : 2). The zones corresponding to the required product were combined and worked up, affording 80 mg of alcohol *XIX* which was crystallized from methanol, m.p. 126 to 128°C, $[\alpha]_D^{20} = -16°$ (*c* 0·5). Infrared spectrum (chloroform): 3 630, 1 028, 1 635, 1 610 cm^{-1}. For $C_{30}H_{50}O$ (426·7) calculated: 84·44% C, 11·81% H; found: 84·15% C, 11·67% H.

4,4-Dimethyl-3α,5-epoxy-A-homo-5α-cholestane (*XXIV*)

Adams catalyst (15 mg) was added to a solution of olefin *XXIII* (20 mg) in ethanol (5 ml) and ethyl acetate (5 ml) and the mixture was shaken under hydrogen for 2 h. The catalyst was filtered off and the filtrate poured into water. The product was extracted with ether, the extract washed with water, dried over sodium sulfate and the solvent evaporated in a vacuum. The residue (20 mg) was crystallized from methanol, affording 16 mg of epoxide *XXIV*, m.p, 97–98°C. Infrared spectrum: 1 019, 1 023 cm^{-1}. For $C_{30}H_{52}O$ (428·7) calculated: 84·04% C; 12·23% H; found: 84·12% C, 12·05% H.

Reaction of Alcohols *XIV* and *XXVI* with Aqueous Perchloric Acid

Perchloric acid (0·04 ml, 72%) in water (0·1 ml) was added to a solution of alcohol (25 mg) in dioxane (2 ml) and the mixture was allowed to stand at room temperature for 3 h. It was poured into water and the product was extracted with ether. The ethereal extract was washed with a 5% aqueous potassium hydrogen carbonate solution and water, dried over sodium sulfate and the solvent evaporated under reduced pressure. The residue was chromatographed on one silica gel thin-layer plate in light petroleum–ether 8 : 2. The required zone was worked up giving 23 mg of alcohol *XIV* or 22 mg of alcohol, *XXVI*, respectively.

The analyses were carried out in the analytical laboratory of this Institute under the direction of Dr J. Horáček. The infrared spectra were measured by Mrs K. Matoušková and interpreted by Dr J. Smolíková. The ^{1}H NMR *spectra were measured by Mrs J. Jelínková. Technical assistance was provided by Mrs M. Bárová.*

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