MASS SPECTRA OF GUAIANOLIDES RELATED TO CHLOROHYSSOPIFOLIN B

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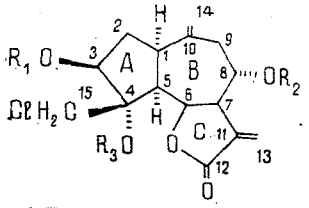
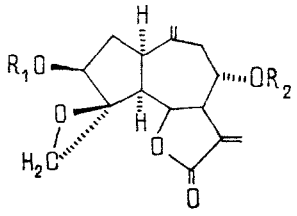
A discussion is given of the fragmentation processes of the guaianolide chlorohyssopifolin B and of eight sesquiterpene lactones related to it with voluminous substituents at C_8 causing instability of the molecular ions. The compositions of the fragmentary ions have been determined and it has been shown that the cleavage of the bonds of ring A takes place only after the elimination of the voluminous substituent. Characteristic for compounds with an exocyclic epoxy group at C_4 is the elimination by the molecular ion in each case of a methoxy radical with the participation of the hydrogen of the C_3 hydroxyl.

The elucidation of the laws of fragmentation of sesquiterpene lactones under electron impact will facilitate the determination of the structures of new compounds. Continuing a study of the spectra of various groups of this fairly diverse class of natural compounds, we previously discussed the mass-spectrometric behavior of certain 1,2-epoxyguaianolides [1, 2]. In the present paper we consider compounds of the guaiane series of the type of chlorohyssopifolin B with a voluminous substituent at C_8 and with an oxirane ring or the product of its hydrochlorination at C_4.

Below we give the formulas and names of the compounds studied.



I, II, IV–VI



VII, VIII, IX

I. $R_1 = R_2 = R_3 = H$ (chlorohyssopifolin B [3, 4]).

II. $R_1 = R_3 = H$; $R_2 = OC{-}C(CH_3){=}CH_2$ (elegin, linichlorin A [5, 6]).

IV. $R_1 = R_3 = H$; $R_2 = OC{-}C(CH_3){-}CH_2Cl$ (hyrcanin, centaurepensin, chlorohyssopifolin A [3, 4, 7, 8]).

V. $R_1 = OC{-}CH_3$; $R_2 = OC{-}\overset{\displaystyle OH}{\overset{|}{C}}(CH_3){-}CH_2Cl$; $R_3 = H$ (hyrcanin monoacetate).

VI. $R_1 = R_3 = OC{-}CH_3$; $R_2 = OC{-}\overset{\displaystyle OCOCH_3}{\overset{|}{C}}(CH_3){-}CH_2Cl$ (hyrcanin triacetate).

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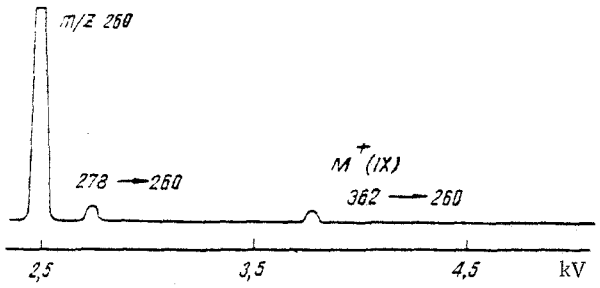


Fig. 1. MD spectrum of the ion with m/z 260 from repin.

VII. $R_1 = H$; $R_2 = OC-C(OH)(CH_3)-CH_2Cl$ (acroptilin, chlorohyssopifolin C [9, 4]).

VIII. $R_1 = OCCH_3$; $R_2 = OC-C(OH)(CH_3)-CH_2Cl$ (acroptilin monoacetate).

IX. $R_1 = H$; $R_2 = OC-C(CH_3)-CH_2-$ (repin [7]).

The main property uniting these substances is the instability of their molecular ions. In publications devoted to establishing the structures of some of these compounds [3, 7, 9], the absence of even an extremely low-intensity peak of M^+ ions is pointed out and the mass numbers of the main characteristic fragmentary ions $(M - R_2OH)^+$ are given. At the same time, it has been shown for the case of hyrcanin (IV) that the detection of M^+ depends on the experimental conditions and, possibly, on the construction of the ion source. Thus, Gonzalez et al.[3] reported the absence of the molecular ion, while Harley-Masson et al. [8] reported the recording of M^+ for hyrcanin.

We have obtained the M^+ peaks of all these compounds with the exception of repin (IX). The molecular mass of the latter was measured by means of the metastable defocusing (MD) method (Fig. 1). The masses of the daughter ions and the directions of fragmentation of the other compounds were checked by the same method.

A second feature of the spectra of the guaianolides, again apparently connected with the experimental conditions is the protonation of the molecular ion (Figs. 2 and 3c, d, e). It has been reported that the height of the $(M + H)^+$ peaks rises with an increase of the pressure in the ion source.

The presence of a voluminous substituent at C_8 in compounds (II-IX) and also of chloromethyl and hydroxy groups at C_4 in (I-VI) leads to a situation in which the cleavage of the bonds of the lactone skeleton takes place after the splitting out of these substituents (scheme). This also explains the presence of strong peaks of fragments in the central part of the spectrum in the interval m/z 175-300. See next page for scheme.

The detachment of small fragments (H_2O, $\dot{C}l$, HCl, $\dot{C}H_2Cl$) directly from M^+ leads to the formation of relatively unstable fragments 2 and 3). A comparison of the spectra of elegin and of acroptilin, and also the results of the MD investigation of these compounds indicates that the detachment of the fragments mentioned takes place both from the nucleus and from the acyl substituent.

Compounds with an oxirane ring at C_4 (VII and IX) are also characterized by the peaks of $(M - 31)^+$ ions. The ratio of the intensities of the polyisotropic peaks of the $(M - 31)^+$ ion in the spectrum of OD-acroptilin corresponds to the presence of one deuterium atom in this ion. This shows the elimination of the epoxy group at C_4 with the participation of the active hydrogen of C_3–OH in the formation of the $(M - 31)^+$ ions. In the spectrum of acrop-

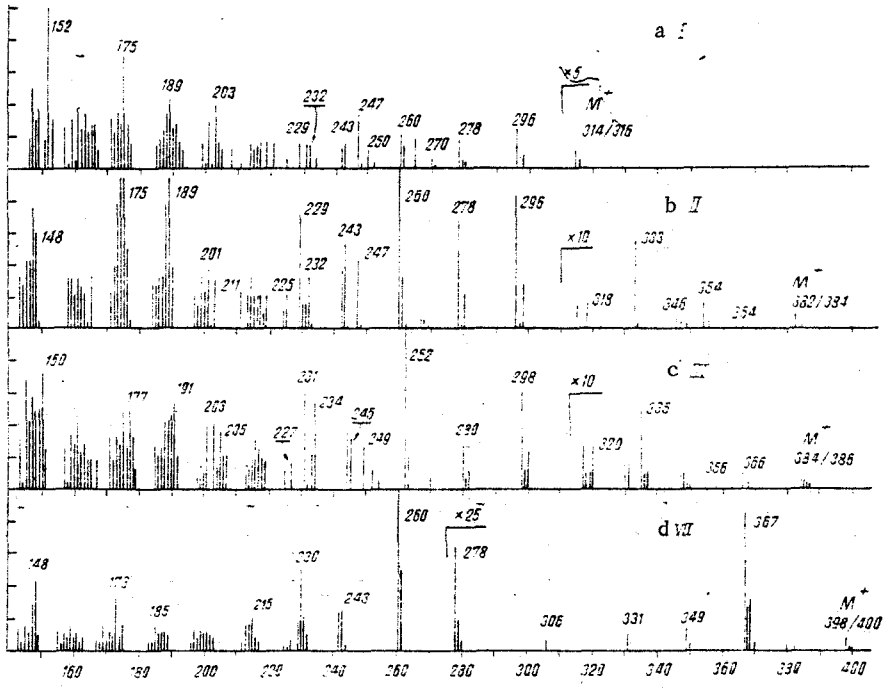
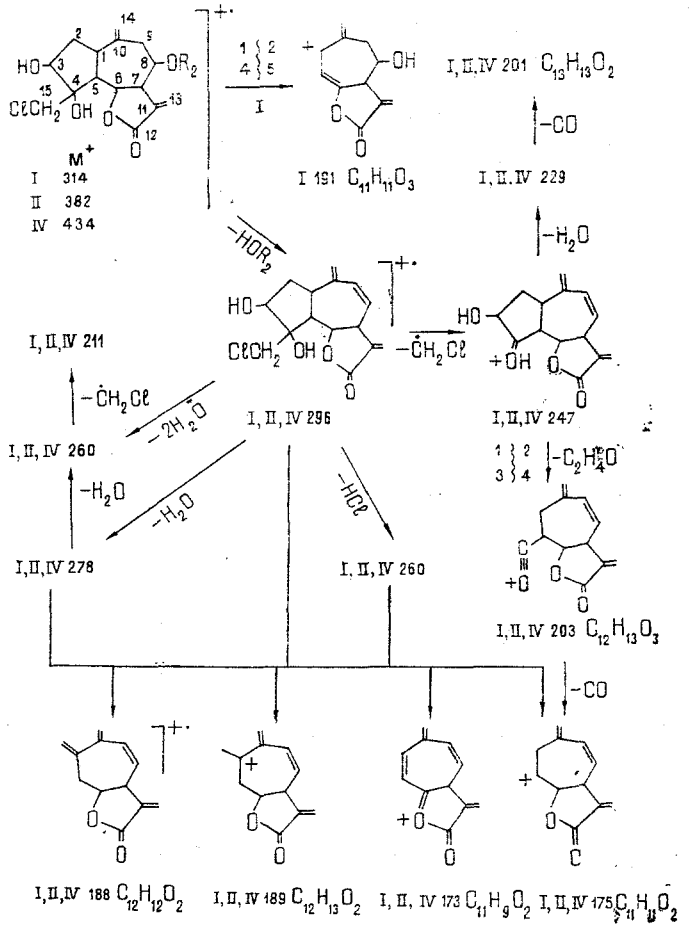


Fig. 2



Scheme 1

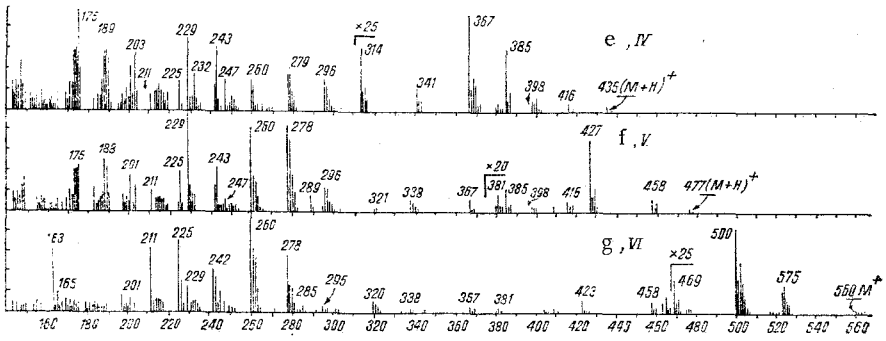


Fig. 3

TABLE 1. Metastable Transitions in the Spectrum of Hyrcanin Monoacetate (V)

Daughter ions													
229	F*	247	F	260	F	278	F	289	F	296	F	338	F
Parental ions													
247	H_2O	365	H_2O	278	H_2O	296	$_2O$	338	CH_2Cl	338	42	356	H_2O
260	CH_3O	289	42	296	HCl	320	42	427	138	356	60	398	60
278	CH_2Cl	367	120	320	60	338	60			416	120	(M^+)	
289	60	385	138	338	$60+H_2O$	416	138			434	138	476	138
338	$60+CH_2Cl$			398	138	458	120+60			(M^+)			
367	138			458	60+138	(M^+)				476	120+60		
427	60+138					476	138+60						

*F — nature or mass of the neutral fragment split out from the parental ion in the given transition.

TABLE 2. Metastable Transitions in the Spectrum of Hyrcanin Triacetate (VI)

Daughter ions													
225	F	242	F	260	F	278	F	320	F	380	F	440	F
Parental ions													
243	H_2O	260	H_2O	278	H_2O	320	42	338	H_2O	422	42	500	60
260	35	278	HCl	320	60	338	60	380	60	(M^+)			
285	60	320	$60+H_2O$	380	60+60	458	80	500	180	560	180		
321	60+HCl	423	181	440	180			(M^+)					
345	60+60	458	180+HCl	500	180+60			560	180+60				
405	180												

tilin monoacetate (VIII), the $(M - 30)^+$ ions are more stable, which confirms the hypothesis put forward. The results of a study of the MD spectra of (VIII) show that a CH_2O fragment is also ejected from the $(M - 42)^+$ and $(M - 60)^+$ ions.

The subsequent alternative elimination of the substituents of the lactone nucleus after the splitting out of the R_2OH leads in the case of compounds (I, II, and IV-VII) to the formation of fragments with m/z 211, 225, 229, 231, 232, 242, 243, 247, and 278, and the spectra of compounds (I, III, IV, and V) contain, in addition, a chlorine-containing ion with m/z 296. The origin of all these fragments was confirmed by measurements of the elementary compositions, and by the MD method (Tables 1 and 2) for the case of the hyrcanin acetates (V) and (VI). In the spectrum of dihydroelegin (hydrogenation of the C_{11}–C_{13} bond), all these fragments are shifted by 2 m.u. in the direction of higher mass numbers. Consequently, the lactone ring C does not take part in these fragmentation processes.

Some complication of the spectrum takes place because of the coincidence of the mass numbers of fragments formed by the loss of HCl, on the one hand, or of $2H_2O$, on the other

TABLE 3. Relative Amounts (%) of Ions of Different Compositions in the Fragments with m/z 260, 278, 279, and 296

m/z	Composition of the ion	Compound I	II	IV	V	VI
260	$C_{15}H_{16}O_4$	75	60	25	20	4
	$C_{15}H_{13}O_3Cl$	25	40	75	80	96
278	$C_{15}H_{18}O_5$	25	0	7	2	0
	$C_{15}H_{15}O_3Cl$	75	100	93	98	100
279	$C_{15}H_{19}O_5$	*	0	5	0	0
	$C_{15}H_{16}O_3Cl$		100	95	100	100
296	$C_{15}H_{17}O_4Cl$	100	100	100	100	*

*Not measured.

hand. In spite of the characteristic ratio of the intensities of the peaks of the ions including the chlorine isotopes, it was more reliable to establish the contribution of the chlorine-containing fragments under high-resolution conditions. Ions with m/z 260, which may arise, for example, from ions with m/z 296 by the loss of $2H_2O$ or of HCl were characterized by an increase in the amount of the chlorine-containing component with an increase in the volume of R_2 in the sequence of compounds (I, II, and IV) (Table 3). An increase in this contribution also takes place in the spectra of the acetates (V) and (VI), but this is already explained by the increase in the stability of the fragments arising with the splitting out of AcOH as compared with the stability of the ions formed by the loss of H_2O.

The main pathway for the formation of the ions with m/z 278 is the dehydration of the ions with m/z 296 (I, II, IV, and V) or the splitting out of AcOH from the ions with m/z 338 (V, VI). At the same time, as can be seen from Table 3, the ion with m/z 278 contains a small halogen-free component the contribution of which is even smaller in the case of hyrcanin (IV) and the monoacetate (V). The appearance of these ions may take place as the result of the splitting out of HCl from the ions $(M - R_2 + H)^+$ with m/z 314 (M^+ in the case of (I)).

In the spectra of hyrcanin (IV) and the monoacetate (V), the intensity of the peaks of the ions with m/z 279 and 297 is increased. The latter are obviously $(M - R_2 - OH)^+$ ions arising directly from the protonated molecular ions.

The appearance in the spectra of acroptilin and repin of the peak of a $(M - R_2 + H)^+$ ion with m/z 278 of low intensity is quite natural.

The halogen-containing component of the ions with m/z 260 in the spectra of (I, II, and IV-VI) breaks down with the loss of $\dot{C}l$ (m/z 225) and of $\dot{C}H_2Cl$ (m/z 211). There is an ion with m/z 225 ($260 - \dot{O}H - H_2O$) in the spectrum of acroptilin and in that of repin, while the ion with m/z 211 is absent, which can be used to establish the nature of a substituent at C_4.

A consideration of the MD spectra of elegin and of hyrcanin shows that the precursors of the ion with m/z 211 are ions with ions with m/z 229, 247, 260, 278, and 296. The latter, in their turn, are formed by the fragmentation of a whole series of parental ions, as can be seen from Tables 1 and 2.

In many cases, the synchronous elimination of several fragments is observed. Thus, in the formation of the ions with m/z 225 of hyrcanin monoacetate, H_2O and $\dot{C}l$ are eliminated simultaneously from ions with m/z 278, and $2H_2O$ and $\dot{C}l$ from ions with m/z 296. Similar processes have been observed by Caspi et al. [10]. Tables 1 and 2 give other reactions of the cleavage of the parental ions as a result of which products of the successive splitting out of the constituents of the lactone nucleus with m/z 260, 247, 243, 242, 229, 225, and 211 are formed (Figs. 2 and 3). The peaks of ions with m/z 231 and 232 arise mainly by the ejection of $\dot{C}OH$ and CO from ions with m/z 260 containing no chlorine atom. In the spectra of acroptilin and repin an ion with m/z 230 appears which arises from ions with m/z 260 by the elimination of a CH_2O molecule at the expense of the oxirane ring at C_4.

Since the interpretation of the spectra in the region of low masses (100-160 m/z) is difficult and has no particular analytical value, we have limited ourselves to a consideration of the peaks of ions in the 210-170 m/z interval. Analysis of the MD results for hyrca-

nin, elegin, and chlorohyssopifolin B shows that it is mainly the $(M - R_2OH)^+$ ions and the products of their fragmentation with m/z 278 and 260 that participate in the formation of these ions. By determining their elementary compositions, we have established that they arise by the breakdown of ring A (scheme), as is also shown by a displacement of the peaks considered by two a.m.u. in the spectrum of dihydroelegin.

Only in the spectrum of chlorohyssopifolin B was an ion with m/z 191 ($C_{11}H_{11}O_3$), formed with the retention of the substituent at C_8, detected.

The appearance in the mass spectra of chlorohyssopifolin B of the 100% peak of the ion with m/z 152 ($C_8H_8O_3$), with the maximum intensity, deserves attention; its formation takes place by the following scheme, as revealed by MD:

$$M^+314(I) \xrightarrow{-HCl} 278^+ \xrightarrow{-CO} 250^+ \xrightarrow{-C_4H_{10}O} 152^+.$$

The intense peak in the spectrum of elegin with m/z 148 proved to be a doublet ($C_{10}H_{12}O$ and $C_9H_8O_2$, 1:3), while in the spectrum of dihydroelegin the contribution of the heavy component to m/z 150, $C_{10}H_{14}O$, had risen to 1:2. The main components of these ions are formed by the ejection of the elements of ring A from the $(M - R_2OH)^+$ fragments. Another feature of the spectrum of dihydroelegin is the appearance of peaks of ions with m/z 207 ($C_{12}H_{12}OCl$ and $C_{12}H_{15}O_3$, 3:1) and 206 ($C_{12}H_{11}OCl$, $C_{12}H_{14}O_3$, and $C_{13}H_{18}O_2$, 1:3:2). The chlorine-containing ions arise as the result of the elimination of R_2OH and $2H_2O$ from M^+ with the subsequent ejection of the elements of the lactone ring C, and the fragments containing three oxygen atoms are likewise formed from the ions $(M - R_2OH)^+$ with the elimination of $2H_2O$ and $\dot{C}H_2Cl$. The appearance of these fragments is obviously due to the saturation of the C_{11}–C_{13} bond.

In the spectra of elegin and of dihydroelegin there are very strong peaks of the acyl ions of methacrylic acid with m/z 69, and an acyl cation with m/z 163/165 is also observed in the spectrum of hyrcanin triacetate.

EXPERIMENTAL

The mass spectra of compounds I and III were obtained on a MKh 1030 instrument (direct introduction of the sample, temperature of the inlet system 120-130°C, ionizing voltage 40 V).

The experiments to record the summary spectra of the lactones of the (IV-IX), to determine the elementary composition of the ions, and to establish the metastable transitions by the method of defocusing the ion beam were carried out on a MKh 1310 high-resolution mass spectrometer (SVP-6 direct inlet system; temperature of the ionization chamber 100-150°C and of the heater tube 100-120°C, ionizing voltage 50 V, acceleration voltage 5 and 2.5 kV).

The exchange deuteration of acroptilin was carried out in CD_3OD.

CONCLUSION

The main directions of the fragmentation of guaianolides with a voluminous substituent at C_8 have been analyzed with the aid of the MD method. The cleavage of the bonds of the skeleton of the five-membered ring A takes place after the elimination of the substituent at C_8.

In the spectra of acroptilin and repin, the elimination of the exocyclic epoxy group in the form of CH_3O with the participation of the active hydrogen of the neighboring OH group is observed.

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TRANSFORMED STEROIDS.

123. SYNTHESIS OF 5α(H)- AND 5α(OH)-6-KETOSTEROIDS WITH AN ADDITIONAL 17α,20ξ-DIHYDROXYTETRAHYDROPYRAN RING E

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The paper is devoted to the synthesis of 3,17α,20-trihydroxy-16β,23-epoxy-21,24-dinor-5αH-cholan-6-one and 3,5α,17α,20-tetrahydroxy-16β,23-epoxy-21,24-dinor-cholan-6-one and derivatives of them. It has been shown that the reduction of 3,17α-dihydroxy-16β,23-epoxy-21,24-dinorchol-5-en-20-one with sodium tetrahydroborate and with diborane takes place stereospecifically with different spatial directivities: in the products of diborane reduction, ring E exists in the boat form, as has been shown by ^1H and ^{13}C NMR methods. The trans linkage of rings A/B in the modified steroids has been confirmed by their circular dichroism spectra.

Continuing investigations into the "structure-function" relationship of polyhydroxysteroids with a tetrahydropyran ring at E, we have synthesized 5α(H)-6-keto and 5α(OH)-6-keto derivatives of 17α,20-diols. The initial compounds for the transformation of ring E and the introduction of the oxygen-containing functions into ring B were the pyranones (I) and (II) [1]. In (I) and (II), ring E was modified by the reduction of the 20-carbonyl group with sodium tetrahydroborate or with diborane. The reduction of (I) and (II) with $NaBH_4$ formed the same 17α,20β-dihydroxy derivative, which was isolated and characterized in the form of the monoacetate (IIIa), the triol (IIIb), the 3,20-diacetate (IIIc), and the 3β,17α,20β-trimethyl ether (IIId). In addition to the saturated diol (IIIa), the reduction of (I) formed as a minor product the allyl alcohol (IV). The position of the C=C double bond in ring E of (IV) was confirmed by its PMR and ^{13}C NMR spectra. The PMR spectrum contained three signals relating to the 20-H, 22-H, and 23-H protons (AMX spin system) and having the following parameters: δ 5.54 ppm, $J_{20,23}$ = 2.6 Hz, $J_{20,23}$ = 2.0 Hz [H(20)], δ 4.65 ppm, $J_{22,20}$ = 2.6 Hz, $J_{22,23}$ = 6 Hz [H(22)], and δ 6.33 ppm, $J_{23,22}$ = 6 Hz, $J_{23,20}$ = 2.0 Hz [H-(23)]. In the ^{13}C NMR spectrum doublets with δ 99.9 and 140.0 ppm corresponded to the C(22) and C(23) carbons.

The introduction of a 5α-hydroxy-6-keto function into ring B of compound (II) and that of (IIIc) was effected by a method which we have developed previously using steroid δ-lactones as examples [2]: by the opening of 5α,6α-epoxides to form 5α,6β-diols and the oxidation of the latter to the desired ketones (VII) and (VIII). See next page for scheme a.

For the synthesis of 6-ketones of the 5-(H) series we used the hydroboration of the tetrahydropyranyl derivative (IIc), obtained by the method of Miashita et al. [3], or of the trimethoxy derivative (IIId). The hydroboration of (IIId) and subsequent oxidation led to the trimethoxy ketone (IX). In the case of (IIc), however, reaction took place at two reaction centers: at the Δ^5 bond and at the 20-keto group, and, as a result, after the elimination of tetrahydropyranyl protection at C-3, oxidation with chromium trioxide in pyridine, and acetylation, the 3β,20α-diacetate (X) was obtained. The axial nature of the proton at C-20 in each of compounds (III), (VIII), and (X) was deduced on the basis of the results of PMR spectroscopy. In all these compounds the 20-H signal has the form of a doublet of dou-

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