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MASS SPECTROMETRY OF STEROID SYSTEMS—III*

NEW APPROACH TO THE CONFIGURATION OF TERTIARY STEROID ALCOHOLS BY MASS SPECTROMETRY

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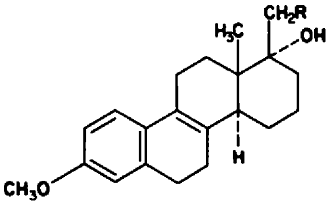
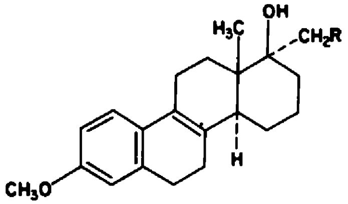
Abstract—A new approach to the configuration of tertiary steroid alcohols is proposed on the basis of comparison of mass spectra of epimeric trideuteromethyl analogues of these compounds.

EARLIER[1] it was shown mass spectrometrically that of the two pairs of epimeric dl-3-methoxy-17a-alkyl-$\Delta^{1,3,5(10),8}$-D-homoestratetraen-17a-ols (Ia,b) (IIa,b), the former possesses the e-alkyl-a-OH configuration at C_{17a}, whereas the latter has the a-alkyl-e-OH configuration at that carbon atom. It was also observed[2] that while the epimers IIa,b readily dehydrate with $POCl_3$ in pyridine at 20°, they are less prone to form M^+—18 fragments under mass spectrometric conditions that the epimers Ia,b which do not dehydrate with $POCl_3$ under similar conditions. It was therefore postulated that the mechanism of dehydration must differ from that obtaining on electron impact.



Ia R=H
Ib R=CH_3



IIa R=H
IIb R=CH_3

In order to elucidate this question we studied the mass spectra of 17a-trideuteromethyl analogues of the Ia and IIa epimers (Ia-CD_3 and IIa-CD_3). A comparison of the mass spectra (Fig. 1a,b) shows that Ia-CD_3 readily dehydrates under electron impact to form essentially only the fragment A_1(M^+—H_2O, m/e 297) with endocyclic

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* Communication I: V. I. Zaretskii, N. S. Wulfson, V. L. Sadovskaya, S. N. Ananchenko, I. V. Torgov, *Dokl. Akad. Nauk SSSR* **158**, 365 (1964); Communication II: N. S. Wulfson, V. I. Zaretskii, V. G. Zaikin, G. M. Segal, I. V. Torgov, T. P. Fradkina, *Tetrahedron Letters* 3015 (1964).

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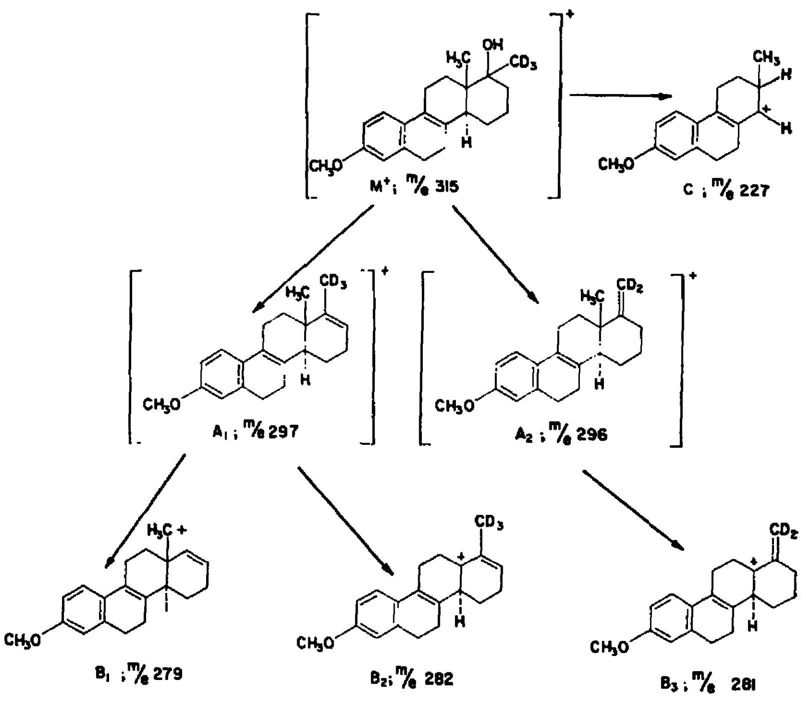
[1] N. S. Wulfson, I. V. Torgov, V. I. Zaretskii, V. N. Leonov, S. N. Ananchenko, V. G. Zaikin, *Izv. Acad Nauk SSSR, Otd. Chim. Nauk* 184 (1964).

[2] S. N. Ananchenko, V. N. Leonov, V. I. Zaretskii, N. S. Wulfson, I. V. Torgov, *Tetrahedron* **20**, 1279 (1964).



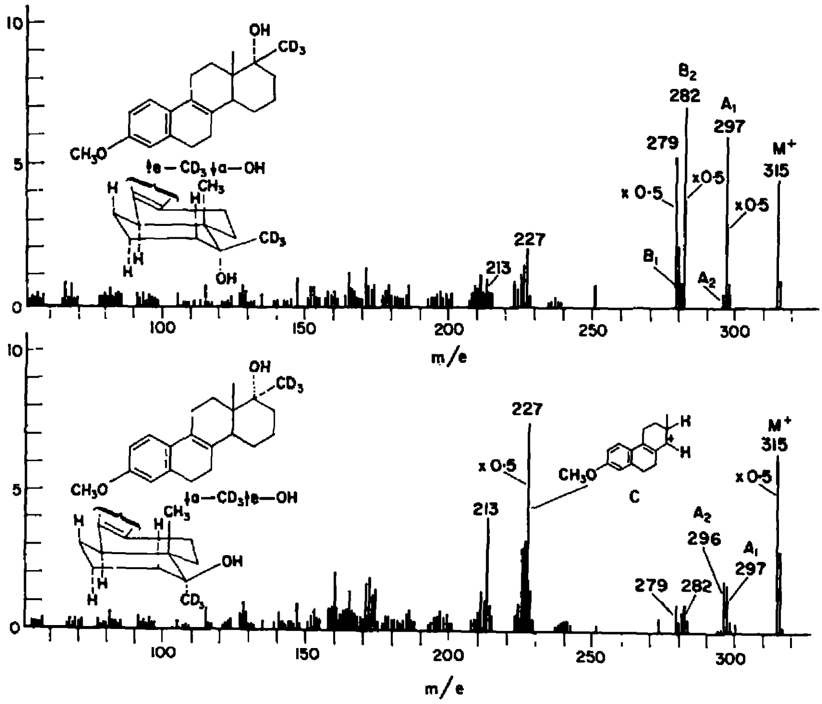


Fig. 1 Mass spectra (direct inlet system) of: (a) Ia-CD_3 and (b) IIa-CD_3

double bond whereas IIa-CD$_3$, dehydrates less readily under these conditions and yields fragments both with endocyclic (A$_1$, m/e 297) and with exocyclic (A$_2$, M$^+$—DOH, m/e 296) double bond (Scheme 1 and Table 1). The formation of fragment A$_1$ instead of A$_2$ from the molecular ion Ia-CD$_3$ bears evidence of the *axial* position of the 17a-OH group in the latter (since only then can one of the *axial* hydrogen atoms of ring D leave together with the OH group) and is therefore additional proof of the configuration at the 17a-centre in this compound. On the other hand the presence of

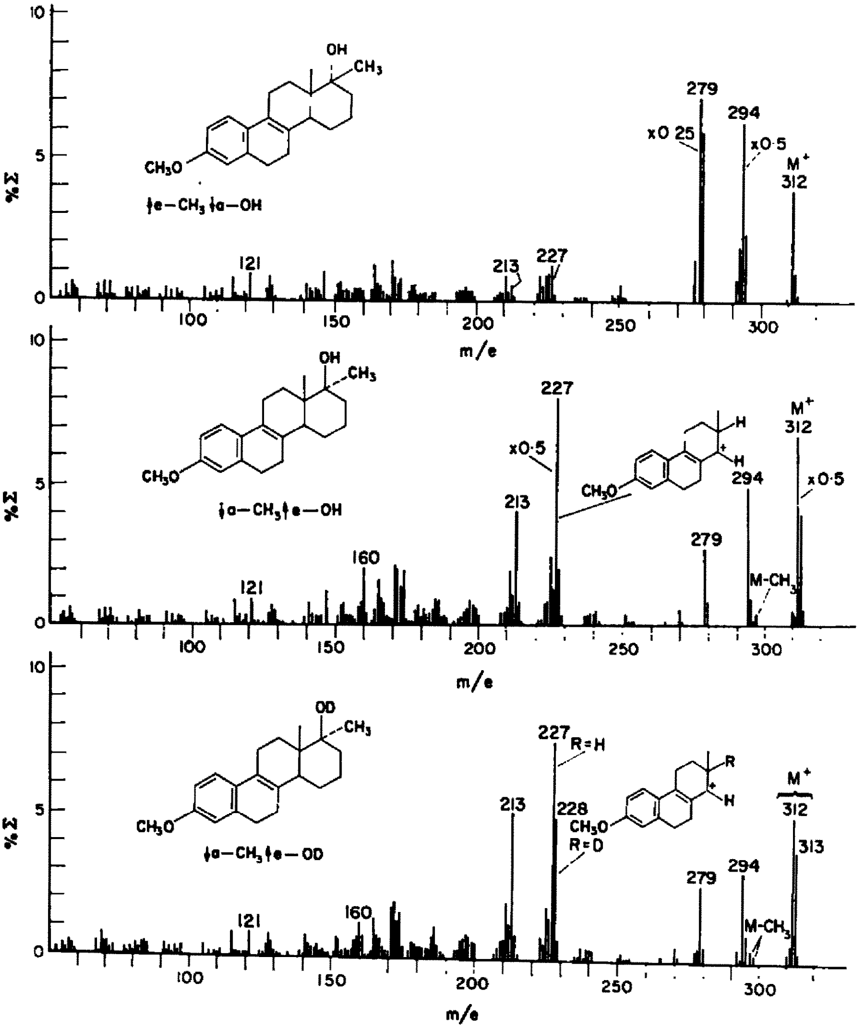


FIG. 2 Mass spectra (direct inlet system) of: (a) Ia, (b) IIa and (c) IIa-OD

approximately equally intensive peaks of the fragments A$_1$(M$^+$—H$_2$O, m/e 297) and A$_2$(M$^+$—DOH, m/e 296) in the mass spectrum of IIa-CO$_3$ indicates the a-alkyl-e-OH-configuration at the 17a centre of this compound.

The results obtained permit a new approach to the determination of the configuration of steroid and possibly other cyclic tertiary alcohols by means of mass spectrometry. Thus the presence of a relatively low intensity doublet in the dehydration peaks of the mass spectrum of the trideuteromethyl tertiary cyclic alcohol, corresponding to the loss of H_2O and DOH and the formation of an endo and exocyclic double bond is a criterion for the a-alkyl-e-OH configuration. On the other hand the presence of an intensive $M^+—H_2O$ peak and a very small $M^+—DOH$ peak in the mass spectra of the same compound is evidence of the e-alkyl-a-OH configuration.

A comparison of the mass spectra of Ia-CD_3, IIa-CD_3 (Fig. 1a,b) with the spectra of the unlabelled epimers Ia and IIa (Fig. 2a,b) shows also the composite nature of the $M^+—H_2O—CH_3$ peak in the spectra of the latter, resulting from fragments of the type B_1, B_2 and B_3 (Scheme 1).

The earlier described[1,2] effect of the configuration of the epimeric alcohols on the intensity of the characteristic peaks in the mass spectra of these compounds obtained in an instrument with metallic inlet system is especially striking when compared with the spectra obtained with a system for introducing the sample directly into the ionic source (Figs. 2a,b, 3a,b and Table 2).

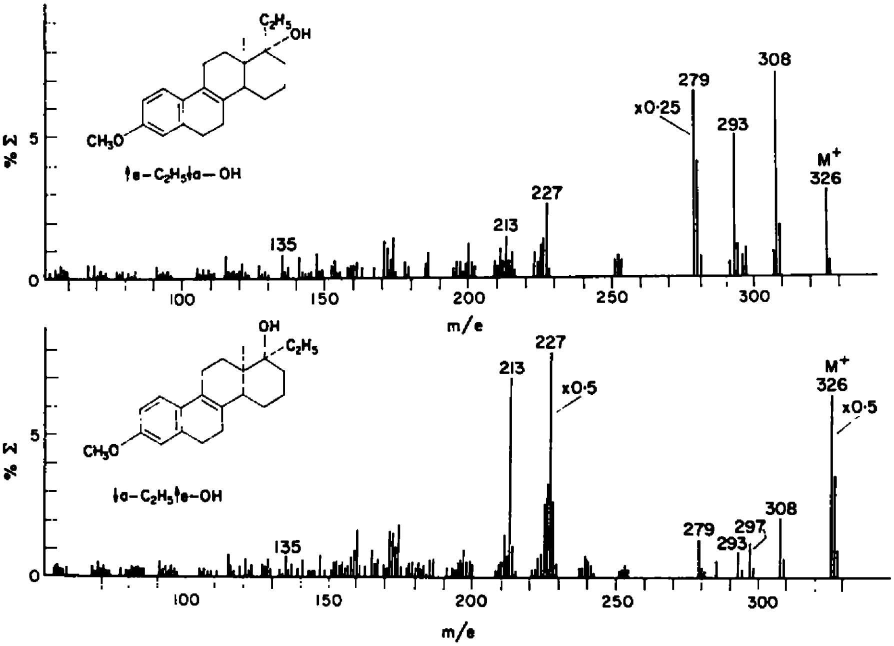


Fig. 3. Mass spectra (direct inlet system) of: (a) Ib and (b) IIb.

It has already been noted[1,2] that one of the peaks whose intensity is characteristic of the configuration of the epimer is that of m/e 227 (fragment C, Scheme 1). It was shown that this fragment is formed directly from the molecular ion as a result of the abstraction of elements of ring D, with subsequent migration of hydrogen atom. The transition $M^+ \rightarrow C$ is confirmed by the corresponding metastable peak appearing at 165 (calc. 165) for Ia and IIa and 158 (calc. 158) for Ib and IIb. In order to elucidate the mechanism of formation of fragment C (and, in particular, the effect of the configuration of the 17a centre) the mass spectrum of the O-deutero-analogue of the epimer IIa (IIa-OD) was obtained. The mass spectrum (Fig. 2c) clearly shows a shift of the fragment C peak by 1 unit (from m/e 227 to m/e 228). This shows that a hydrogen of the hydroxyl group takes part in the formation of the rearranging fragment C and that consequently the difference in the intensity of this peak (m/e 227) among the epimers is connected with their configuration (the hydrogen migrates more easily from the equatorial group than from the axial). The data obtained also makes it possible to assume that the migration hydrogen adds to the C_{13} atom, whereas the positive charge is on the C_{14} atom instead of on the C_{13} atom as postulated earlier,[1] since in the case of migration of the hydrogen to the C_{14} atom the 17a *axial* OH group would be closer than the *equatorial* OH, so that the intensity of the C fragment in the spectrum of the Ia epimer would be greater than that of the IIa epimer. The formation of a positive charge on the C_{14} atom apparently contributes to the stabilization of fragment C owing to the possibility of delocalization of the charge by the conjugated double bond system.

TABLE 1

Compound	M^+	%Σ				
		m/e 297 $M-H_2O$	m/e 296 $M-DOH$	m/e 282 $M-H_2O-CH_3$	m/e 279 $M-H_2O-CD_3$	m/e 281 $M-DOH-CH_3$
Ia-CD_3 e-CD_3 a-OH	4·7	12·3	0·5	14·5	10·8	0·9
IIa-CD_3 a-CD_3 e-OH	13	1·8	1·9	1·0	1·0	0·7
		$\frac{M-H_2O}{M}$	$\frac{M-DOH}{M}$	$\frac{M-H_2O-CH_3}{M}$	$\frac{M-H_2O-CD_3}{M}$	$\frac{M-DOH-CH_3}{M}$
Ia-CD_3 e-CD_3 a-OH		2·6	0·1	3·1	2·3	0·2
IIa-CD_3 a-CD_3 e-OH		0·14	0·14	0·08	0·08	0·05

TABLE 2

Compound	%Σ				m/e 227	$\frac{M-18}{M}$	$\frac{m/e\ 279}{M}$
	M^+	M—18	m/e 279 M—18—15	m/e 279 M—18—29			
Ia e-CH_3 a-OH	4·0	12·6	28·8	—	1·2	3·2	7·2
IIa a-CH_3 e-OH	13·4	4·8	2·8	—	16	0·4	0·2
Ib e-C_2H_5 a-OH	3·2	7·3	—	26	2·6	2·3	8·2
IIb a-C_2H_5 e-OH	13	2·3	—	1·4	16	0·2	0·1

EXPERIMENTAL

Preparation of IIa-OD. The compound IIa-OD was prepared by keeping IIa in a solution of C_2H_5OD for 3 hr, following which the solution containing a mixture of IIa and IIa-OD was used directly in the mass spectrometric run.

Preparation of the epimers Ia-CD_3 *and* IIa-CD_3. The epimers Ia-CD_3 (m.p. 112–113; from CH_3OH) and IIa-CD_3 (m.p. 121–123; from CH_3OH) were synthesized by reaction of CD_3MgI with the methyl ether of 8,9-dehydro-D-homoestrone in benzene–ether solution according to the procedure described.[3]

The mass spectra were obtained with the instrument MX-1303 furnished with a glass inlet system allowing the sample to be charged directly into the ion source near the ionization chamber (direct inlet system) at a temp of 100–120° (±1·0°) and ionization energy 70 ev.

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[3] S. N. Ananchenko, V. M. Rzheznikov, V. N. Leonov, I. V. Torgov, *Izv. Akad. Nauk SSSR, Otd. Chim. Nauk* 1913 (1961); S. N. Ananchenko, V. E. Limanov, V. N. Leonov, V. M. Rzheznikov, I. V. Torgov, *Tetrahedron* **18**, 1355 (1962).