Tetrahedron. Vol. 23, pp. 3683 to 3686. Pergamon Press Ltd. 1967. Printed in Great Britain

MASS SPECTROMETRY OF STEROID SYSTEMS—X[*]

DETERMINATION OF THE CONFIGURATION AT C-17 IN THE PREGNENE-3,20-DIONE SERIES

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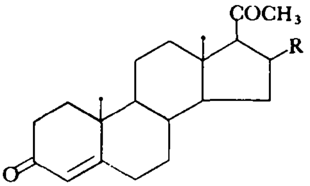
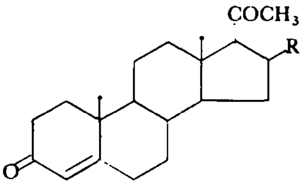
(*Received* 30 *November* 1966; *accepted for publication* 4 *January* 1967)

Abstract—The mass spectra of progesterone, 17-isoprogesterone and their 16 β-methyl derivatives were measured. The presence of 17α-acetyl group causes intensive rupture of the 15–16 and 13–17 bonds resulting in formation of the ions at *m/e* 244 and 71 (or 85).

IN THE foregoing papers of this series we have shown mass spectrometry to be useful for the determination of the hydroxyl group configuration in steroid alcohols[1–3] as well as the mode of ring fusion in *cis* and *trans* isomers of steroids, terpenoids and related compounds.[4–6] We have now studied the mass spectra of Δ^4-pregnene-3,20-diones epimeric at the 17 centre as these are of both chemical and biological interest. Progesterone (Ia), 17-isoprogesterone (IIa) and their 16β-methyl derivatives (Ib and IIb) are the subjects of the present investigation.



Ia: R = H
Ib: R = CH$_3$



IIa: R = H
IIb: R = CH$_3$

A comparison of the mass spectra of the epimeric pairs (Figs. 1(a, b), 2(a, b) and Table 1) reveals that they have the same pathways of fragmentation, but differ strongly

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[*] Part IX: N. S. Wulfson, V. I. Zaretskii, V. L. Sadovskaya, A. V. Zakharichev, S. N. Ananchenko and I. V. Torgov, *Tetrahedron* **23**, 3667 (1967).

[1] V. I. Zaretskii, N. S. Wulfson, V. G. Zaikin, S. N. Ananchenko, V. N. Leonov and I. V. Torgov, *Tetrahedron* **21**, 2769 (1965).

[2] V. I. Zaretskii, N. S. Wulfson, V. G. Zaikin, L. M. Kogan, N. E. Voishvillo and I. V. Torgov, *Tetrahedron* **22**, 1399 (1966).

[3] V. I. Zaretskii, N. S. Wulfson, V. G. Zaikin, V. N. Leonov, S. N. Ananchenko and I. V. Torgov, *Tetrahedron Letters* 347 (1966).

[4] N. S. Wulfson, V. I. Zaretskii, V. L. Sadovskaya, A. V. Semenovsky, W. A. Smit and V. F. Kucherov, *Tetrahedron* **22**, 603 (1966).

[5] N. S. Wulfson, V. I. Zaretskii, V. L. Sadovskaya, S. N. Ananchenko, V. M. Rzheznikov and I. V. Torgov, *Tetrahedron* **22**, 1885 (1966).

[6] N. S. Wulfson, V. I. Zaretskii and V. L. Sadovskaya, *Tetrahedron Letters* 3879 (1966).

in the intensities of corresponding characteristic peaks. The largest difference is observed in the intensity of the *m/e* 244 peak, formed by cleavage of the 15–16 and 13–17 bonds and elimination of carbon atoms 16, 17, 20 and 21. This is supported by the shift of this peak by 5 units (to *m/e* 249) in the spectrum of progesterone-d_9 (distribution of d-atoms in its molecule is established on the basis of the shifts of the corresponding peaks, c.f.[7] and Fig. 1(b, c), whereas no shift of this peak is observed in the spectra of 16-methyl derivatives (Ib and IIb). The peaks at *m/e* 71 (for Ia and IIa) and 85 (for Ib and IIb) which are much more pronounced in the spectra of

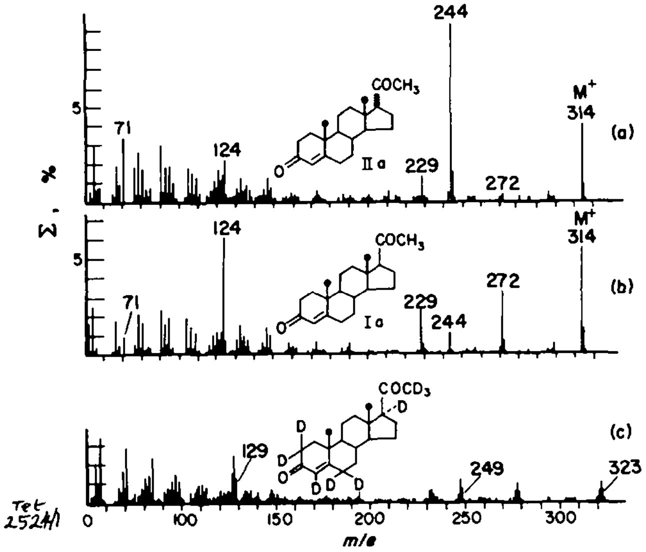


Fig. 1. Mass spectra of: (*a*) 17-isoprogesterone (IIa), (*b*) progesterone (Ia), (*c*) progesterone-d_9.

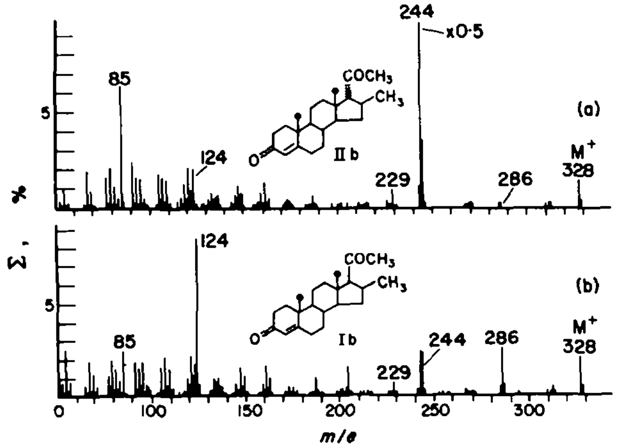


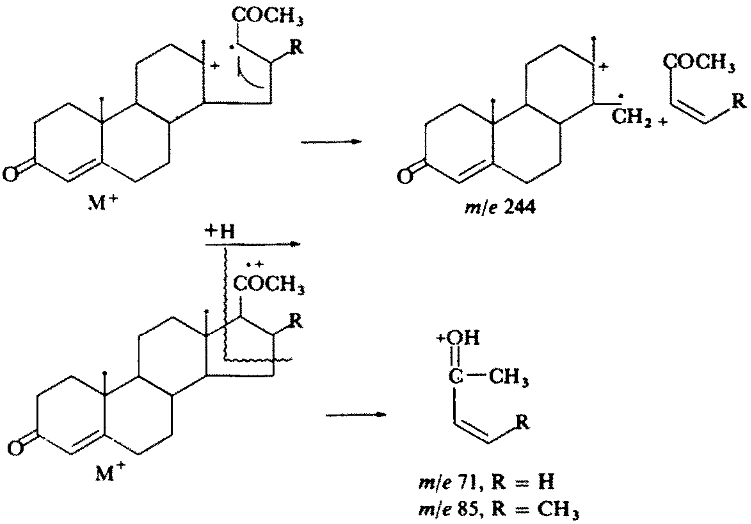
Fig. 2 Mass spectra of: (*a*) 16β-methyl-17-isoprogesterone (IIb), (*b*) 16β-methylprogesterone (Ib).

[7] R. H. Shapiro and C. Djerassi, *J. Am. Chem. Soc.* **86**, 2825 (1964).

TABLE 1. INTENSITIES OF CHARACTERISTIC PEAKS (% OF TOTAL IONIZATION) IN THE MASS SPECTRA OF IA, B AND IIA, B

Compound	M^+	m/e 244	m/e 71 (or 85)	$\frac{m/e\ 244}{M^+}$	$\frac{m/e\ 71\ (\text{or } 85)}{M^+}$
Ia, 17β-Ac	5·7	1·2	1·0	0·2	0·17
IIa, 17α-Ac	4·2	9·4	3·4	2·2	0·8
Ib, 17β-Ac	2·3	2·3	2·6	1·0	1·1
IIb, 17α-Ac	1·7	19·8	6·5	11·6	3·8

17α-epimers are also due to rupture of the 13–17 and 15–16 bonds accompanied by hydrogen migration to the charged fragment. The origin of the *m/e* 71 ion is confirmed by the shift of its peak mass number by 14 units in the spectra of Ib and IIb and by 28 units in the spectrum of 16,17-dimethylprogesterone (obtained by Maximov *et al.*[8]).



It is difficult to explain the much greater intensity of the *m/e* 244 and 71 (or 85) peaks in the mass spectra of 17α-epimers when compared with their 17β-analogues. However, a suggestion may be put forward that the presence of 17α-acetyl group results in increased strain in ring D and, hence, in easier elimination of C_{16} and C_{17} atoms. This hypothesis is corroborated by the fact that in the spectrum of 17α-methylprogesterone the *m/e* 244 peak is also predominant. Nevertheless, it remains unclear why the decomposition leading to formation of the tricyclic fragment at *m/e* 229 is not stimulated in this case. The latter process is known to be characteristic of many steroid systems.[9]

[8] V. I. Maximov, V. M. Potapov, F. A. Lurji, A. M. Muchnikova, S. L. Portnova and L. S. Morozova, *Zh. Obshch Khim.* in press.

[9] H. Budzikiewicz, C. Djerassi and D. H. Williams, *Structure Elucidation of Natural Products by Mass Spectrometry* Vol. 2; p. 94. Holden-Day, San Francisco, Calif. (1964).

It should be mentioned that the intensity of the *m/e* 124 and M-42 peaks which are characteristic of Δ^4-3-oxosteroids[7] is strongly decreased in the mass spectra of 17α-epimers when compared with 17β-compounds. This is apparently because the energetically more favourable process results in formation of the *m/e* 244 ion instead.

An easier elimination of C-atoms 16 and 17 with substituents (here it takes place from the M-18 ion) in the case of 17α-isomers when compared with their 17β-analogues is also confirmed by analysis of the mass spectra taken by Tschesche.[10]

In order to elucidate the effect of the configuration at position 16 on the fragmentation of pregnene-3,20-dione derivatives, the mass spectrum of 16α-epimer of Ib was measured. However, the spectra of Ib and its 16α-epimer appeared to be identical.

EXPERIMENTAL

The mass spectra of the compounds under investigation were obtained on the commercial instrument MX-1303, furnished with a system allowing direct sample inlet into the ion source, at 125° (±1°) and ionizing energy 70 eV.

Progesterone-d_9

Progesterone-d_9 was obtained by 3 hr boiling of progesterone (20 mg) in a mixture of dry THF (4 ml), D_2O (0·1 ml), EtOD (0·5 ml) and Na (4 mg) and after usual procedure was used directly in the mass spectrometric run.

Acknowledgements—The authors express deep gratitude to Dr. Leonid M. Kogan for a sample of Ia and Dr. V. I. Maximov for samples of Ib, IIb, 16α-isomer of Ib and 16,17-dimethylprogesterone.

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[10] R. Tschesche, P. Welzel and H.-W. Fehlhaber, *Tetrahedron*, **21**, 1797 (1965).