STEROIDS, XXII

Comparative Study of Oxime-Forming Reactions of Steroid-17-ketones, II (Short Communication)

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The thermodinamic indices of the oxime-forming reactions of various hormone-active androgenic steroid-17-ketones and their derivatives were compared. In order to establish correlations involving the thermodinamic parameters, five androgen-active and ten oestrogen-active 17-ketosteroids were examined.

In the first part of this work the kinetic parameters of the oxime-forming reactions of several steroid ketones were compared with the kinetic parameters of various alicyclic ketones, and the order of oxime-forming reaction (under the conditions applied) was elucidated [1].

In the present paper we deal only with an internal comparison of the thermodynamic parameters of the steroid-17-ketones.

The substances examined were classified into groups according to the basic skeleton. The first group consisted of androgen-active epi- and dehydroepiandosterone* derivatives, while the second group was made up of a wide range of oestrone derivatives (ethers, esters) with female sex hormone effects.

Experimental

For purposes of exact comparison, the methods described in Part I were used. Ketones were employed in a concentration of 10^{-3} mole, dissolved in a 2:1 mixture of chloroform—methanol.

Oxime-formation was achieved with a 0.005 mole hydroxylamine salicylate solution in chloroform—methanol (2:1). The residual hydroxylamine salicylate was back-titrated with a 0.005 *N* HCl solution in propane-1,2-diol—chloroform (1:1), in the presence of a mixture of dimethyl yellow and methylene blue as indicator [2]. The measurements were made in the temperature range 30—50 °C.

* Abbreviations used: DEA = dehydroepiandrosterone (3β-hydroxyandrost-5-en-17-on); DEA-acet. = dehydroepiandrosterone-3β-acetate; DEA-benz. = dehydroepiandrosterone-3β-benzoate; Cl-DEA = 3β-chlorodehydroepiandrosterone; EPA = epiandrosterone (3β-hydroxy-5α-androstan-17-one); Oe = oesterone (3-hydroxyoestra-2,4,5(10)-trien-17-one); Oe-Me-ether = oestrone-3-methyl ether; etc.

The starting steroids were made available for experimental purposes by the G. RICHTER Pharmaceutical Works (Budapest). They were purified by recrystallization and layer-chromatography. Both compounds and all of the 17-ketones (synthesized by methods reported earlier) were used in the purest possible form [3, 4].

The logarithm of the rate constant was plotted as a function of the inverse of temperature; applying the equation given previously [1], the activation enthalpy ($\Delta H^{\ddagger}$) and activation entropy ($\Delta S^{\ddagger}$) were calculated from the slopes and intercepts of the curves, respectively.

The data were processed with a MINSK-22 computer.

Results and discussion

The $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values of EPA, DEA and their derivatives are given in Table I. Table II lists the same thermodynamic parameters for Oe, its ethers and its esters.

By comparing the data in Table I it can be seen that the $\Delta S^{\ddagger}$ values show considerable differences.

Of the androgens listed EPA is the most active, while there is no great difference between the androgenic activities of DEA and its derivatives.

The thermodynamic values calculated from the kinetic constants in Table II similarly embrace a wide range. The activation enthalpies can be divided roughly into two groups: values above, and below 10 kcal/mole. The sequence for the compounds in the latter group is: Oe-isoPr ether < Oe-benzoate < Oe-acetate < Oe < Oe-allyl ether, while in the other group the sequence is: Oe-Bu ether < Oe-benzyl ether < Oe-cyclopentylether < Oe-Me ether < Oe-Et ether. The situation is different in the case of the activation entropies. Here the value for Oe differs substantially from those for its derivatives, though the influence of the substituents on the reactions of the C-17 keto group clearly appears.

Our results prove convincingly the correlation assumed in Part I [1], namely that the substituents at C-3 markedly affect the reactions of the C-17 keto group. In our experience the effects of the substituents can be correlated with their electrochemical properties.

Table I

	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ kcal/mole. degree
DEA	6.19	−48.44
DEA-acet.	7.09	−46.61
Cl-DEA	8.23	−43.01
DEA-benz.	12.25	−31.80
EPA	15.51	−20.42

Table II

	$\Delta H^{\ddagger}$ kcal/mole	$\Delta S^{\ddagger}$ kcal/mole. degree
Oe	7.70	− 9.32
Oe-Me ether	14.08	−26.87
Oe-Et ether	14.30	−22.12
Oe-acetate	6.04	−49.81
Oe-isoPr ether	4.92	−19.51
Oe-Bu ether	10.81	−36.74
Oe-allyl ether	9.69	−38.89
Oe-cyclopentyl ether	12.48	−28.69
Oe-benzyl ether	11.02	−34.38
Oe-benzoate	4.99	−54.29

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СТЕРОИДЫ, XXII
СРАВНИТЕЛЬНОЕ ИЗУЧЕНИЕ ОКСИМООБРАЗУЮЩИХ РЕАКЦИЙ СТЕРОИД-17-КЕТОНОВ, II

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Определены термодинамические параметры реакции оксимообразования некоторых стероидных кетонов, обладающих гормональной активностью. Стероид-17-кетоны и их производные в основном обладали острогенными свойствами и лишь некоторые имели андрогенные свойства. Изучена взаимосвязь термодинамических параметров пяти стероидов с андрогенным и десяти стероидов с острогенным гормональным действием.