

STEROIDS. XI

Bromination of Some Δ_5 -Unsaturated Steroids

By J. A. SZABÓ and M. HALMOS

Institute of Organic Chemistry Attila József University, Szeged

P. WINKLER

Central Research Institute for Chemistry, Hungarian Academy of Sciences, Budapest

(Received May 2, 1968)

The rate of bromination of some Δ_5 -unsaturated steroids was measured at 16° and 23° and the approximate activation parameters were calculated from the data obtained. The values for free energy of activation were found to be near constant.

Recently a number of publications have appeared concerning the effect of substituents far from the reaction centre upon the rate of reaction [1—8]. These long-range effects can readily be examined in such systems, not too flexible from a conformational point of view, as terpenoids [2, 3, 4] and steroids [1, 6]. As BARTON and coworkers [3] stated the phenomenon can not be accounted for merely by polar and conformational effects, though both participate. On examining the bromination reaction of Δ_5 -substituted steroids SCHWARZ and coworkers [6, 7, 8] found a relationship between the pK_a value of the acid esterifying the 3β -hydroxy group and the logarithm of the rate constant of the reaction, which referred to the primary character of polar effects.

In the course of the examinations reported so far the conclusions were drawn mainly from experimental data obtained at a single temperature value only. In order to study the effect of temperature factors the bromination reaction of some Δ_5 -unsaturated steroid derivatives, available in the authors' laboratory, was studied under conditions somewhat different of those applied by SCHWARZ [6]. The bromination of the following steroid derivatives was studied: pregnenolone (II), 17α -hydroxypregnenolone (Ia), 17α -hydroxypregnenolone 3-acetate (Ib), solasodine (VIIIa), dehydroepiandrosterone acetate (III), O,N-diacetylsolasodine (VIIIb), 16α -cyanopregn-5-ene- $3\beta,20\beta$ -diol (IV), 16β -carboxy- 17α -(iso)-pregn-5-ene- 3β -ol-20-one (V), 16β -carboxypregn-5-ene- $3\beta,20\beta$ -diol-16,20-lactone 3-acetate (VI) and cholesterol acetate (VII). The data calculated from the experimental results are enlisted in Table I. All reactions were followed until no formation of by-products could be detected by thin-layer chromatography (Merck, Kieselgel G adsorbent).

Table I includes relative rate constants, too, based on 17α -hydroxypregnenolone 3-acetate (Ib), which was taken as 100, both at 16° and 23°. The rate constant of this compound (Ib) was measured at further two temperature values. As the table shows, in case of two compounds (Ia and VIIIb) the rate of reaction was too high to be followed by the method applied.

Table I

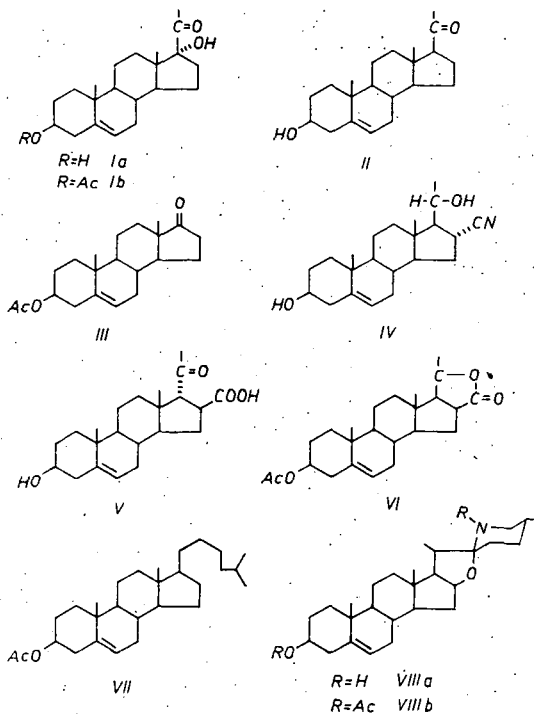
Compound	$k_{10^{\circ}}$ l/mol. sec.	$k_{rel10^{\circ}}$	$k_{23^{\circ}}$ l/mol. sec.	$k_{rel23^{\circ}}$	H_{act}^* kcal/mol	S_{act}^* entropy unit	G_{act}^* kcal/mol
pregnenolone (II)	29,5	1201	21,6	713	-7,5	-79,5	16,2
solasodine (VIIIa)	10,8	438	8,9	295	-4,5	-70,9	16,5
O,N-diacetylsolasodine (VIIIb)	very fast reaction, unfollowable by the technique applied						
cholesterol acetate (VII)	9,6	390	6,5	215	-9,3	-87,5	16,7
17 α -hydroxypregnenolone (Ia)	very fast reaction, unfollowable by the technique applied						
17 α -hydroxypregnenolone 3-acetate (Ib)**	2,5	100	3,2	100	5,1	-38,7	16,9
dehydroepiandrosterone acetate (III)	1,6	66	1,3	44	-4,4	-75,0	17,8
16 α -cyanopregn-5-ene-3 β ,20 β -diol(IV)	6,4	260	8,5	281	7,0	-32,3	16,5
16 β -carboxy-17 α -(iso)-pregn-5-ene-3 β -ol-20-one (V)	1,2	50	3,4	112	24,7	25,7	17,3
16 β -carboxypregn-5-ene-3 β ,20 β -diol 16,20-lactone 3-acetate (VI)***			1,7	56			

* values calculated from two data

** $k_{10^{\circ}}$ 2,7 l/mol.sec., $k_{21^{\circ}}$ 2,9 l/mol.sec.

*** measured at 23° only

The changes in the rate constants *vs.* temperature are considerable and they do not follow exactly the polarity of the respective groups. Changes in the 3-hydroxy function exert particularly substantial effect upon the reaction rate.



On the basis of the rate constants at the two different temperatures approximate activation parameters were calculated. Of these, the calculated approximate free energy of activation appears to be almost constant (cca. 16—17 kcal/mol) and it is in good agreement with the observations of WALLISCH and DUBOIS [9].

Experimental

Materials

Commercial chloroform was shaken successively with concd. sulphuric acid, water, dilute Na_2CO_3 solution and water, dried over anhydrous $CaCl_2$ and distilled from P_2O_5 . The 1st and last 1/5 fractions were discarded. Commercial glacial acetic acid was refluxed with chromic acid for two hours and distilled, the 1st and last 1/5 fractions being again discarded. Neither of the two solvents was further specified.

The physical constants and analytical data of the steroid derivatives were in good agreement with literary data.

Measurements

The reactions were carried out in an ultrathermostat, where the desired temperature could be maintained with an accuracy of $\pm 0.1^\circ$. Twenty ml. of the standard steroid solution in chloroform (containing cca. 60 mg. steroid) was mixed at the given temperature with 0.05 N bromine in glacial acetic acid solution corresponding to 50% excess of bromine. Subsequent to the reaction time aqueous KI solution was added and the iodine content titrated with 0.05N $\text{Na}_2\text{S}_2\text{O}_3$ solution. Five parallel measurements were carried out for each temperature and reaction period values, respectively.

Calculations

The rate constants were calculated from the half-time of the reactions, the latter being determined graphically. In all cases the ratio of half and third periods corresponded to second-order reaction. The approximate activation parameters were calculated in the usual way [10, 11].

References

- [1] Grob, C. A., S. Winstein: *Helv. chim. Acta* **35**, 785 (1952).
- [2] Barton D. H. R., A. J. Head: *J. Chem. Soc.* **1956**, 932.
- [3] Barton D. H. R., A. J. Head, P. J. May: *J. Chem. Soc.*, **1957**, 935.
- [4] Barton D. H. R., F. McCapra, P. J. May, F. Thudium: *J. Chem. Soc.*, **1960**, 1297.
- [5] Schwarz, V., J. Trojanek: *Coll. Czech. Comm.*, **26**, 117 (1961).
- [6] Schwarz, V., S. Hermanek, J. Trojanek: *Coll. Czech. Comm.* **26**, 1438 (1961).
- [7] Schwarz, V., S. Hermanek, J. Trojanek: *Coll. Czech. Comm.* **27**, 2778 (1962).
- [8] Schwarz, V., S. Hermanek: *Coll. Czech. Comm.* **29**, 2360 (1964).
- [9] Wallisch, W., J. E. Dubois: *Chem. Ber.* **92**, 1028 (1959).
- [10] Benson, S. W.: *The Foundations of Chemical Kinetics* (McGraw-Hill, New York, 1960).
- [11] Schlaeger, L. L., F. A. Long: *Entropies of Activation and Mechanism of Reactions in Solution*, in Gold. V.: *Advances in Physical Organic Chemistry Vol. 1* (Academic Press, London, New York, 1963).

СТЕРОИДЫ. XI ИЗУЧЕНИЕ БРОМИРОВАНИИ НЕКОТОРЫХ Δ_5 -СТЕРОИДОВ

И. А. Сабо, М. Гальмош и П. Винклер

Авторы измерили скорость бромирования некоторых Δ_5 -стероидов при температурах 16 и 23 °C и из экспериментальных данных исчислили активационные параметры. Данные активационных свободных энтальпий были почти постоянные.