11-Oxygenated Steroids. V. The Preparation of 11α-Hydroxypregnanes[1]

By Eugene P. Oliveto, Hershel L. Herzog and E. B. Hershberg

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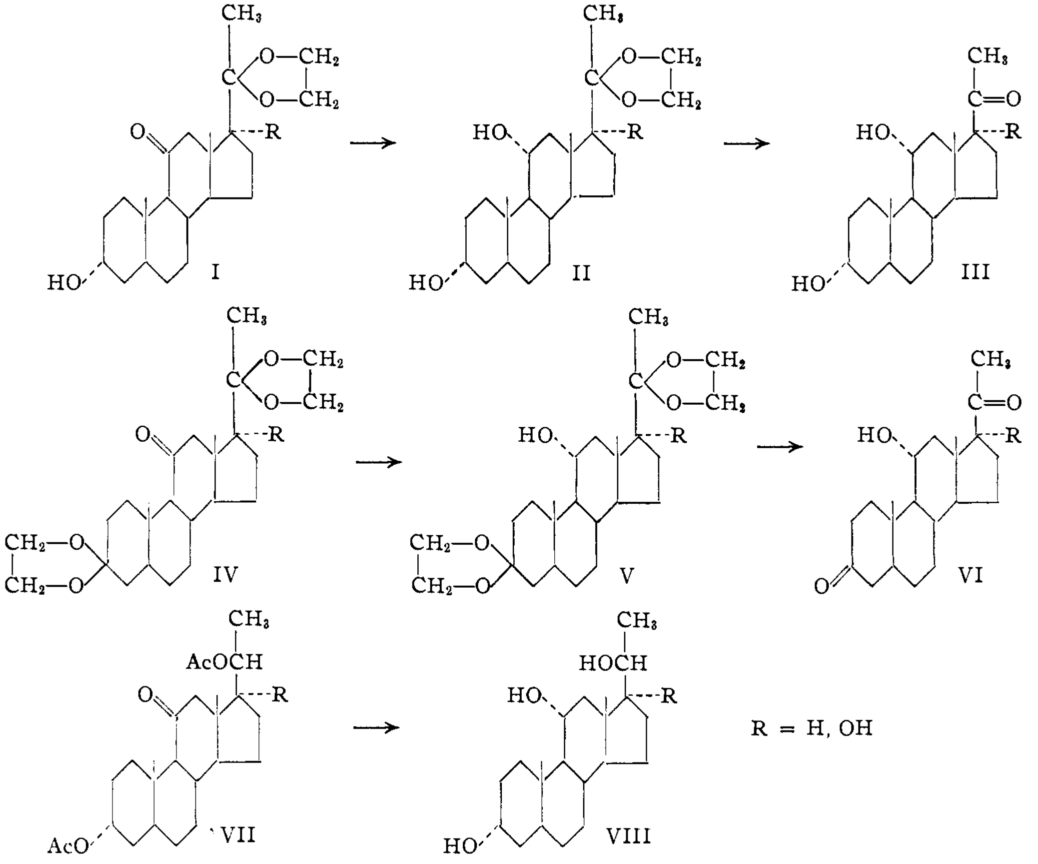
The recent discovery[2] that 11-ketosteroids can be reduced to the corresponding 11α-hydroxysteroids in excellent yield by means of sodium in boiling 1-propanol has led to a simple and convenient method for the preparation of 11α-hydroxypregnanes, most of which have been prepared for the first time.

The appropriate pregnan-11,20-dione or -3,11,20-trione was converted to the 20-ethylene ketal (I) or 3,20-bis-ethylene ketal (IV) by means of ethylene glycol.[3] Sodium in refluxing propanol converted the free 11-ketone to an 11α-hydroxyl in excellent yield, and hydrolysis of the ketals with dilute mineral acid[2c] or aqueous acetic acid[3] generated the 11α-hydroxy ketones (III and VI):



An alternate method for preparing the 3,20-diketo-11α-hydroxypregnanes made use of the relative inertness[2a,2c] of the 11α-hydroxyl group toward mild oxidizing agents. Thus, N-bromoacetamide oxidation of pregnan-3α,11α-diol-20-one (III, R = H) and pregnan-3α,11α,17α-triol-20-one (III, R = OH) produced the corresponding 3-ketones (VI) in good yield.

Pregnan-3α,20β-diol-11-one 3,20-diacetate (VII, R = H) and pregnan-3α,17α,20β-triol-11-one 3,20-diacetate[1] (VII, R = OH) were both reduced by sodium and 1-propanol to the free 3α,11α,20β-triol (VIII, R = H) and 3α,11α,17α,20β-tetrol (VIII, R = OH), respectively.

Experimental[4]

The preparation of pregnan-3α-ol-11,20-dione 20-ethylene ketal, pregnan-3α,17α-diol-11,20-dione 20-ethylene ketal, pregnan-3,11,20-trione 3,20-bis-ethylene ketal, pregnan-17α-ol-3,11,20-trione 3,20-bis-ethylene ketal, pregnan-3α,20β-diol-11-one diacetate and pregnan-3α,17α,20β-triol-11-one, 3,20-diacetate has been reported previously.[1,3]

The sodium reduction was carried out by dissolving the steroid in approximately 50 volumes of *n*-propyl alcohol, heating the solution to reflux, and adding 5 times the weight of sodium as rapidly as possible. Refluxing was continued for 0.5 hour whereupon an equal volume of methanol was added. When all the sodium had reacted, about 0.5 the volume of water was added, and then steam introduced to distil off the alcohols. The reduced dioxolanes precipitated and after removal by filtration, were crystallized from the appropriate solvents.

The ketal groups were split off by hot aqueous acetic acid[3] or by acetone and dilute hydrochloric acid.[2c]

N-Bromoacetamide oxidations of pregnan-3α,11α-diol-20-one and pregnan-3α,11α,17α-triol-20-one were carried out in the usual manner[2c] in aqueous acetone for two hours in the ice-box. Yields were 85–90%.

In one case, the intermediate V (R = H) was difficult to crystallize, so that pregnan-3,11,20-trione 3,20-bis-ethylene

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[1] Part IV, E. P. Oliveto and E. B. Hershberg, This Journal, **75**, 488 (1953).

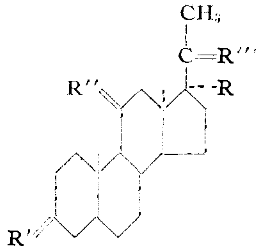
[2] (a) Hershel L. Herzog, Eugene P. Oliveto, Margaret A. Jevnik and E. B. Hershberg, *ibid.*, **74**, 4470 (1952); (b) H. Heusser, R. Anliker, and O. Jeger, *Helv. Chim. Acta*, **35**, 1537 (1952); (c) Hershel L. Herzog, Margaret A. Jevnik and E. B. Hershberg, This Journal, **75**, 269 (1953).

[3] Eugene P. Oliveto, Temple Clayton and E. B. Hershberg, *ibid.*, **75**, 486 (1953).

[4] All m.ps. are corrected. All rotations were taken in a one decimeter tube at a concentration of about 1%. We are indebted to Mr. Edwin Conner, Mrs. Alice Barella, Mrs. Beatrice Grebe, Mrs. Elizabeth McEntire and Miss Joan Mustachio for the analytical and rotational data.

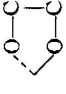
TABLE I

PHYSICAL CONSTANTS AND YIELD DATA



R'	R''	R'''	Yield, %	M.p., °C.	[α]D	Empirical formula	Anal. Carbon, % Calcd.	Anal. Carbon, % Found	Anal. Hydrogen, % Calcd.	Anal. Hydrogen, % Found	Recrystallization solvent
	R = H										
OH H	OH H	O—CH$_2$ O—CH$_2$	97	199.0–199.8	+19.8°	$C_{23}H_{38}O_4$	72.97	72.86	10.12	10.41	Acetone–hexane
OH H	OH H	O	90	181.4–182.4	+89.4	$C_{21}H_{34}O_3$	75.40	75.19	10.25	10.29	Acetone–hexane
OAc H	OAc H	O	..	147.0–148.0	+74.3[a]	$C_{25}H_{38}O_5$	71.74	71.95	9.15	9.40	Ether–hexane
OH H	OH H	OHβ H	92	186.5–187.8	− 9.9[b]	$C_{21}H_{36}O_3$	74.94	74.75	10.78	11.02	Acetone
OAc H	OAc H	OAcβ H	..	259–262	+25.2[b]	$C_{27}H_{42}O_6$	70.10	70.16	9.15	9.36	Acetone
O—CH$_2$ O—CH$_2$	OH H	O—CH$_2$ O—CH$_2$	Not isolated								
O	OH H	O	80	108.0–110.0[c]	+89.0	$C_{21}H_{32}O_3$	75.86	76.05	9.70	10.05	Hexane
O	OAc H	O	..	149.4–150.8[d]	+51.8	$C_{23}H_{34}O_4$	73.76	73.59	9.15	8.96	Hexane
	R = OH										
OH H	OH H	O—CH$_2$ O—CH$_2$	97	213.2–214.0	−13.3	$C_{23}H_{38}O_5$	70.01	69.70	9.71	9.74	Methanol–water
OH H	OH H	O	94	Solvated	+25.8	$C_{21}H_{34}O_4 \cdot H_2O$	68.44	68.14	9.85	10.07	Acetone–water
OAc H	OAc H	O	..	190.2–191.4	+21.7	$C_{25}H_{38}O_6$	69.09	68.80	8.81	9.09	Acetone–water
OH H	OH H	OHβ H	90	238–241	−19.7[b]	$C_{21}H_{36}O_4$	71.55	71.34	10.29	10.24	Methanol–water

TABLE I (*Continued*)

R′	R″	R‴	Yield, %	M.p., °C.	$[\alpha]_D$	Empirical formula	Carbon, % Calcd.	Carbon, % Found	Hodrogen, % Calcd.	Hodrogen, % Found	Recrystallization solvent
	R = H										
			..	277–278	+ 5.2^a	$C_{27}H_{42}O_7$	67.75	68.06	8.85	9.04	Methanol
			98	109.5–111.5	−10.8	$C_{25}H_{40}O_6$	68.77	68.42	9.24	9.50	Acetone-hexane
O		O	92	192.6–194.0	+21.3	$C_{21}H_{32}O_4$	72.38	72.62	9.26	9.49	Acetone-water
O		O	..	204.4–206.2	− 1.4	$C_{23}H_{34}O_5$	70.74	70.95	8.78	8.85	Acetone-water

All rotations are in acetone, except those noted. ^{a} Chloroform. ^{b} Dioxane. ^{c} Reported m.p. 116–118°, $[\alpha]_D$ +91° ($CHCl_3$) [O. Mancera, A. Zaffaroni, B. Rubin, F. Sondheimer, G. Rosenkrantz and C. Djerassi, THIS JOURNAL, 74, 3711 (1952)]; m.p. 102–105°, $[\alpha]_D$ +83° ($CHCl_3$) [H. Murray and D. Peterson, U. S. 2,602,769]. ^{d} Reported m.p. 148–149°, $[\alpha]_D$ +65° ($CHCl_3$) [Djerassi, *et al.*, ref. *c*].

ketal (IV, R = H) was converted to pregnan-11α-ol-3,20-dione (VI, R = H) without isolation of pregnan-11α-ol-3,20-dione 3,20-bis-ethylene ketal (V, R = H).

Acetates were prepared by the usual procedure with acetic anhydride and pyridine.

Physical constants and yield data are recorded in Table I.

CHEMICAL RESEARCH DIVISION
SCHERING CORPORATION
BLOOMFIELD, N. J.

On the Relation between Spectral Changes and *p*H of the Anthocyanin Pelargonidin 3-Monoglucoside[1]

BY ERNEST SONDHEIMER

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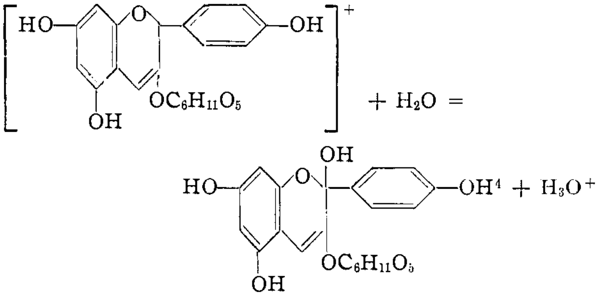
The predominant effect of increasing hydrogen ion activity on the spectral properties of pelargonidin 3-monoglucoside is an increase in the intensity of absorption in the visible region.[2] Furthermore, on the addition of water to unbuffered benzopyrylium salt solutions a decrease in the light absorption in the visible range is observed which is greater than can be accounted for merely by dilution effects. These observations can be explained by the hypothesis that there is an equilibrium between hydronium ions, a red modification R^+ and a colorless form ROH of the anthocyanin. Evidence for this view is presented below. The method used here has previously been applied to many acid–base indicators but not to anthocyanins.[3]

The hydrolysis reaction may be shown as



then

$$pK = \log \frac{R^+}{ROH} + pH$$

In Table I the effects of changes in the *p*H on the light absorption at 500 millimicrons and on the *pK* values are shown. For the *p*H range in which the R^+ concentration varies between 98.4 and 10.8% the *pK* is constant within the experimental error. Thus one of the conditions necessary to consider this as an equilibrium reaction has been met. This evidence is strengthened by the observations that the *pK* is independent of the anthocyanin concentration and that the equilibrium may be approached from either side. The isolation of color-

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[1] Journal Article No. 908, New York State Agricultural Experiment Station.

[2] E. Sondheimer and Z. I. Kertesz, THIS JOURNAL, **70**, 3476 (1948).

[3] I. M. Kolthoff "Acid–Base Indicators," translated by Ch. Rosenblum, The Macmillan Co., New York, N. Y., 1937.

[4] Although the pseudo-base is here represented as a 2-chromenol it is not known whether this is the predominant tautomer. J. A. Berson, THIS JOURNAL, **74**, 358 (1952), has shown that with some triphenylpyrylium pseudo-bases the open-chain 1,5-diketone was the only tautomer whose presence could be demonstrated.