Notes

Esters of Some Steroidal 3β-Hydroxy-4,6-dienes and their Biological Activity

JOHN S. BARAN

Division of Chemical Research, G. D. Searle & Co., Chicago 80, Illinois

Received December 24, 1962

It has been established that in biologically and clinically active steroids the introduction of a double bond at C_6[1] or the transformation of a C_3-ketone to a 3β-acetoxyl derivative[2] does not significantly alter biological activity. Because of such evidence and a continuous effort in these laboratories to obtain structure and activity relationships among steroids, an investigation was undertaken into the synthesis and biological activity of esters of some steroidal 3β-hydroxy-4 6-dienes.

Chemistry.—The steroidal 3β-hydroxy 4-6-dienes were prepared by the reduction of the corresponding C_3-ketones with lithium tri-*tert*-butoxy aluminum hydride in tetrahydrofuran at 25.[3] Treatment of the 3β-hydroxy derivatives with acetic or propionic anhydride in pyridine yielded the respective acyl derivatives in good yields. 6-Dehydro-17-ethynyltestosterone was prepared by the dehydrogenation of 17-ethynyltestosterone with chloranil.[4]

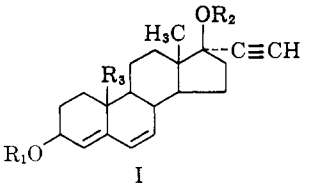
Biology.—Table I summarizes the biological activities of the compounds described herein. These data demonstrate again that biological activity is not significantly altered when a biologically active 3-keto-steroid is transformed to its 3β-hydroxy or 3β-acetoxy derivative.

Experimental

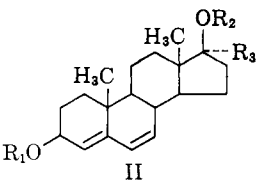
General Procedure for the Reduction of the Steroidal 3-Keto-4,6-dienes with Lithium Tri-*tert*-butoxyaluminum Hydride.—To a solution of 1 g. of the steroidal 3-keto-4,6-diene in about 50 ml. of dry tetrahydrofuran was added 2 g. of lithium tri-*tert*-butoxyaluminum hydride. The solution was stirred at room temperature for 1 hr., cooled to about 5°, and then diluted carefully with 100 ml. of 20% aqueous acetic acid. The mixture was then extracted with 200 ml. of chloroform. The chloroform solution was washed successively with 100 ml. of 1% aqueous acetic acid, two 100-ml. portions of water and saturated sodium bicarbonate and then dried over sodium sulfate and distiled to dryness *in vacuo*. If the residue was not crystalline, trituration of the residue with ether or ether and Skellysolve B yielded a crystalline product. The yields of crude crystalline product ranged from 40–95%.

TABLE I[a]

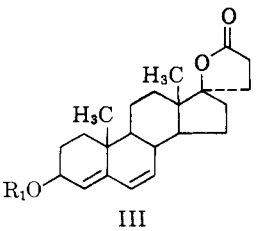
BIOLOGICAL ACTIVITIES



I



II



III

Compound	R_1	R_2	R_3	% Progestational activity in Clausberg assay[b] Oral	Subcutaneous
Ia	H	H	CH_3	0	
Ib	H	Ac	CH_3	5	
Ic	Ac	H	CH_3	5	
Id	COC_2H_5	H	CH_3	5	
Ie	Ac	Ac	CH_3	0	
If	H	Ac	H	10	100
Ig	Ac	Ac	H	—	100
6-Dehydro-17-ethynyl-19-nortestosterone 17-Acetate[c]				100	250
6-Dehydro-17-ethynyltestosterone				5	
6-Dehydro-17-ethynyltestosterone 17-Acetate				5	

	R_1	R_2	R_3	% Androgenic activity	% Myotropic[d] activity
IIa	H	Ac	H	2	<2
IIb	Ac	Ac	H	1	<2
IIc	H	H	CH_3	5	5
IId	Ac	H	CH_3	5	<2
IIe	COC_2H_5	H	CH_3	0	<2
6-Dehydro-17-methyltestosterone				—[e]	—[e]

		DCA blocking activity (M.E.D.)[f] Subcutaneous
IIIa	H	1.2 mg.
IIIb	Ac	0.72 mg.
IIIc	COC_2H_5	>2.4 mg.
3-(3-Oxo-17β-hydroxy-4,6-androstadien-17α-yl) propionic acid lactone[g]		0.6 mg.

[a] The author is indebted to Drs. R. L. Elton, F. J. Saunders, and C. Kagawa of the Biological research staff, G. D. Searle and Co., for the biology reported herein. [b] C. W. Emmons, "Hormone Assay," Academic Press, Inc., New York, N. Y., 1950, p. 422. All values are compared to subcutaneous progesterone. [c] F. B. Colton, U. S. Patent 2,946,809 (July 26, 1960). [d] E. Eisenberg and G. S. Gordon, *J. Pharmacol. Exptl. Therap.*, 99, 38 (1950). All values compared to subcutaneous testosterone propionate. [e] This compound was predominantly myotropic and weakly androgenic in activity. R. O. Clinton, A. J. Mason, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Am. Chem. Soc.*, 81, 1513 (1959). [f] C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, 126, 1015 (1957). [g] See ref. 1 (d).

(1) (a) H. J. Ringold, E. Bates, A. Bowers, and J. Edwards, *J. Am. Chem. Soc.*, **81**, 3485 (1959); (b) P. Sollman, R. L. Elton, and R. M. Dodson, *ibid.*, **81**, 4435 (1959); (c) L. H. Knox, J. Zderic, J. P. Ruelas, C. Djerassi, and H. J. Ringold, *ibid.*, **82**, 1232 (1960); (d) J. A. Cella, *J. Org. Chem.*, **24**, 1109 (1959).

(2) (a) S. Bernstein, *ibid.*, **22**, 472 (1957); (b) F. B. Colton and P. D. Klimstra, *Excerpta Medica Intern. Congress Series, Intern. Congress on Hormonal Steroids*, Milan, 1962, paper no. 48.

(3) It is assumed that the reduction of a 3-keto-4,6-diene proceeds in an analogous manner to the reduction of the 3-keto-4-ene system to give the 3β-hydroxy derivative, preponderantly or exclusively. See O. H. Wheeler and J. Matteos, *Chem. Ind.* (London), 395 (1957), and footnote 2 (b).

(4) E. J. Agnello and G. D. Laubach, *J. Am. Chem. Soc.*, **79**, 1257 (1957).

TABLE II[a]

ANALYTICAL DATA

Compound	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	$[\alpha]_D^{25}$b
Ia	220–221	$C_{20}H_{28}O_2$	80.73	80.84	9.06	9.23	−152°[b]
Ib	138–140	$C_{21}H_{30}O_2$	77.93	78.24	8.53	8.22	−148°[b]
Ic	125–132	$C_{21}H_{30}O_3$	77.53	77.69	8.53	8.35	−102°[b]
Id	117–118	$C_{23}H_{34}O_3$	78.22	78.09	8.75	8.60	−103°[b]
Ie	165–166	$C_{23}H_{32}O_3$	75.72	75.31	8.13	7.96	−113°[b]
If	186–183	$C_{22}H_{32}O_3$	77.61	77.10	8.29	8.27	−130°[b]
Ig	188–190	$C_{21}H_{30}O_4$	75.86	75.98	7.91	7.92	−105°[b]
IIa	147–148	$C_{21}H_{30}O_2$	76.4	76.55	9.18	8.96	−55°[c]
IIb	169–170	$C_{22}H_{32}O_2$	71.16	71.12	8.66	8.73	−83°[c]
IIc	235	$C_{20}H_{28}O_2$	79.5	79.33	10.0	9.64	−98°[c]
IId	139–140	$C_{22}H_{32}O_3$	75.80	77.18	9.49	9.55	−90°[c]
IIe	99–100	$C_{21}H_{30}O_3$	77.4	76.74	9.58	9.57	...[c]
IIIa	179–184	$C_{23}H_{34}O_2$	77.0	77.06	8.87	8.96	−71°[c]
IIIb	165–166	$C_{24}H_{36}O_2$	71.97	71.18	8.35	8.33	−91°[c]
IIIc	158–160	$C_{24}H_{34}O_3$	75.4	75.71	8.62	8.73	−92°[c]

[a] Melting points were determined on a Fisher-Johns block and are corrected. Rotations were obtained in chloroform unless otherwise noted. The analytical data were reported by Dr. R. T. Dillon and his staff at G. D. Searle & Co. [b] Pyridine. [c] Methanol.

Acylation of the 3β-Hydroxy Steroids.—A solution of 1 g. of 3β-hydroxy steroid, 5 ml. of pyridine, and 2.5 ml. of acetic or propionic anhydride was allowed to stand at 25° for 1 day. The solution was then slowly diluted at 0° with water. The crystalline precipitate which appeared was collected by filtration and dried *in vacuo*. The yields of crude product ranged between 85 and 98%. An analytical sample was prepared by crystallization of the crude product from ether and Skellysolve B or acetone and Skellysolve B.

6-Dehydro-17-ethynyltestosterone 17-Acetate.—A solution of 200 mg. of 6-dehydro-17-ethynyltestosterone, 5 ml. of pyridine, and 2 ml. of acetic anhydride was refluxed for 2 hr., cooled to 0°, diluted slowly with water, and then extracted with ether. The ether solution was washed successively with dilute hydrochloric acid, water and aqueous sodium bicarbonate and then dried over sodium sulfate and distilled to dryness *in vacuo*. The residue upon crystallization from ether and Skellysolve B yielded 150 mg. (72%) of the product which melted at 145–146°, λ_{max}^{MeOH} 282.5 mμ (ε 26,300), $[\alpha]_D^{25}$ −80° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.70; H, 8.17.

Synthesis of Some Steroidal [3,2-d]- and [17,16-d]-2′,6′- Diaminopyrimidines

LELAND L. SMITH, DANIEL M. TELLER, AND THEODORE FOELL

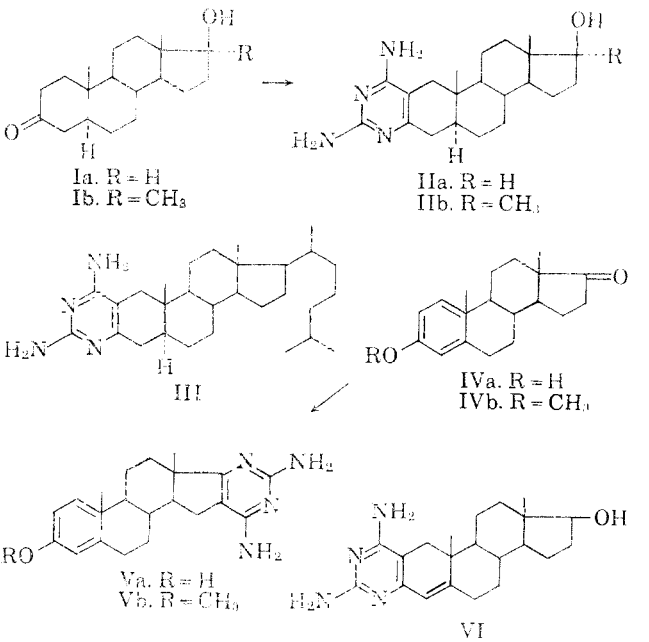
Research and Development Division, Wyeth Laboratories, Inc., Radnor, Pa.

Received November 13, 1962

In view of recent pharmaceutical interest in steroids bearing heterocycles fused to the A- or D-ring of the steroid nucleus, we wished to synthesize steroids fused in the 2,3- and 16,17-positions to the pyrimidine ring system. The tetrahydroquinazoline synthesis of Appelquist,[1-3] employing a fusion reaction between cyanoguanidine and an appropriate cyclic ketone, formed the basis for our studies. Since the inception of this work several reports of different types of A-ring steroidal pyrimidines prepared by other methods[4-6] have appeared.

Reaction of a series of 4,5α-dihydro-3-ketosteroids with cyanoguanidine gave the anticipated steroido-[3,2-d]-2′,6′-diaminopyrimidines. Thus, 4,5α-dihydrotestosterone (Ia), 17α-methyl-4,5α-dihydrotestosterone (Ib), and 5α-cholestan-3-one gave 17β-hydroxy-5α-androstano-[3,2-d]2′,6′-diaminopyrimidine (IIa), 17β-hydroxy-17α-methyl-5α-androstano-[3,2-d]-2′,6′-diaminopyrimidine (IIb), and 5α-cholestano-[3,2-d]-2′,6′-diaminopyrimidine (IIc), respectively.

The reaction also took place with 17-ketones; thus estrone (IVa) gave 3-hydroxy-1,3,5(10)-estratrieno-[17,16-d]-2′,6′-diaminopyrimidine (Va) and estrone methyl ether (IVb) gave its respective pyrimidine Vb. Partial reaction occurred with dehydroisoandrosterone, but the product was not isolated and characterized. Reaction with testosterone gave a major product formulated as the pyrimidine VI.



The steroids II and V absorb characteristically at 283–284 mμ (ε 5000–8000) and near 230 mμ (ε 8000–16,000) in ethanol. For the dihydrotestosterone derivatives IIa and IIb the spectra were not materially changed in alkaline ethanol; however, in acidified ethanol the 230 mμ band was missing and the 284 mμ band was shifted to 273 mμ. This behavior is very similar to that of 2,4-diaminopyrimidine[7] and 2,4-diamino-5,6,7,8-tetrahydroquinazoline.[3] Other 4-aminopyrimidine derivatives behave similarly, and may lose their long wave length absorption band (present in neutral solution) on acidification, either by a substantial hypsochromic shift or by consolidation with shorter wave length absorption.[8] The diaminopyrim-

(1) A. J. Appelquist, U. S. Patent 2,517,824 (August 8, 1950).

(2) (a) E. J. Modest, S. Chatterjee, H. Kangur, and D. M. Brun, Abstracts of Papers 137th American Chemical Society National Meeting, Cleveland, Ohio, April 5–14, 1960, p. 4N; (b) E. J. Modest, H. Kangur, and S. Chatterjee, Abstracts of Papers, 141st American Chemical Society National Meeting, Washington, D. C., March 20–29, 1962, p. 26N; (c) E. J. Modest, S. Chatterjee, and H. Kangur, *J. Org. Chem.*, **27**, 2708 (1962).

(3) J. DeGraw, L. Goodman, B. Weinstein, and B. R. Baker, *ibid.*, **27**, 576 (1962).

(4) (a) J. A. Zderic, O. Halpern, H. Carnes, A. Ruiz, D. C. Linton, L. Magaña, H. Jiménez, A. Bowers, and H. J. Ringold, *Chem. Ind.* (London), 1625 (1960); (b) H. J. Ringold, J. A. Zderic, C. Djerassi, and A. Bowers, U. S. Patent 3,026,317 (March 20, 1962).

(5) F. B. Colton and I. Laos, U. S. Patent 2,999,092 (Sept. 5, 1961).

(6) P. De Ruggieri, C. Gandolfi, and D. Chiaramonte, *Gazz. Chim. Ital.*, **92**, 768 (1962).

(7) M. M. Stimson, *J. phys. radium*, **15**, 390 (1954).

(8) (a) R. R. Williams, A. D. Rueble, and J. Finkelstein, *J. Am. Chem. Soc.*, **59**, 526 (1937); (b) L. F. Cavalieri, A. Bendich, J. F. Tinker, and G. B. Brown, *ibid.*, **70**, 3875 (1948); (c) L. Cavalieri and A. Bendich, *ibid.*, **72**, 2587 (1950); (d) M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 3716 (1952); (e) D. J. Brown and L. N. Short, *ibid.*, 331 (1953); (f) E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951); (g) P. B. Russell and G. H. Hitchings, *ibid.*, **73**, 3763 (1951).