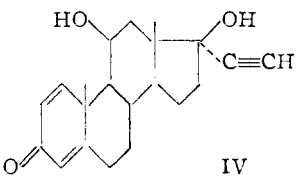
ETHYNYLATED DERIVATIVES RELATED TO ADRENOSTERONE AND A STEROIDAL EFFECT ON EXPERIMENTAL HYPERLIPAEMIA

Sir:

The recent communication of Marshall, Riegel *et al.*[1] on 11-oxygenated 17α-ethynyl, -vinyl and -ethyl testosterones, prompts us to publish the result of a work[2] on the ethynylation of steroids derived from Δ^4-androstene-3,11,17-trione (adrenosterone), which provides several compounds described herein, whose physiological study has been undertaken in our laboratory.

The first published 17α-ethynylated derivatives from the 17-ketosteroids related to testosterone were obtained by condensation of acetylene on a 3β-hydroxy 17-ketosteroid, using potassium in liquid ammonia,[3] sometimes followed by an Oppenauer oxidation. Stavely[4] prepared 17α-ethynyl-Δ^5-androstene-3,17-diol by condensing acetylene in the presence of potassium tertiary amylate and Inhoffen[5] extended this procedure to the 3,17-diones whose 3-keto group previously has been protected as the enol ether.

We have prepared ethynylated derivatives from adrenosterone[6] and 3,11,17-triketo-$\Delta^{1,4}$-androstadiene,[7] without protecting the 3-keto group nor making use of liquid ammonia, by condensation with acetylene in the presence of potassium tertiary amylate at room temperature. The ethynylated derivatives I and II, thus obtained, lead to the corresponding 11β-hydroxy compounds III and IV, by reduction of the 11-keto group with borohydride, the 3-keto group having been protected previously by semicarbazide. Compounds III and IV may also be obtained by direct ethynylation of 11-dihydroadrenosterone[8] and 3,17-diketo-11β-hydroxy-$\Delta^{1,4}$-androstadiene.[7]



IV

(I): m.p. 303°, $[\alpha]_D$ +110° (*c* 0.5 in dioxane), λ_{max} 238 mμ (ϵ 15,300) (EtOH). Infrared maxima ($CHCl_3$) at 1618, 1665, 1705, 3310, 3600 cm.$^{-1}$. Found: C, 77.3; H, 8.2.

(II): m.p. 253°, $[\alpha]_D$ +80° (*c* 1), λ_{max} 238 mμ (ϵ 13,600). Infrared maxima at 1605, 1622, 1663, 1708, 3310, 3600 cm.$^{-1}$. Found: C, 77.6; H, 7.4.

(III): m.p. 283°, $[\alpha]_D$ +55° (*c* 0.5), λ_{max} 242 mμ (ϵ 15,800). Infrared maxima at 1618, 1663, 3310, 3600 cm.$^{-1}$. Found: C, 76.6; H, 8.6.

(IV): m.p. 289°, $[\alpha]_D$ 0° (*c* 0.5), λ_{max} 242 mμ (ϵ 14,650). Infrared maxima at 1606, 1621, 1662, 3310, 3600 cm.$^{-1}$. Found: C, 77.4; H, 8.2.

We have studied the effect of 3-keto-11β,17β-dihydroxy-17α-ethynyl-$\Delta^{1,4}$-androstadiene (IV) on experimental hyperlipaemia and have noted its clarifying action on blood plasma. Compound IV was given orally to dogs (5–10 mg./kg.) on an hyperlipaemizing diet (10 g./kg. of milk-cream) and the blood plasma turbidity measured 3, 5 and 7 hours after treatment. The values noted under these conditions and those obtained in the Kunkel test were much lower than the data of control series of dogs on the same diet, but without IV, as indicated in Tables I and II.

TABLE I

BLOOD PLASMA TURBIDITY

Time, hr.	Untreated (10 dogs)	Treated (10 dogs)
0	0.36	0.34
3	1.68	.91
5	2.20	.85
7	1.35	.61

TABLE II

BLOOD PLASMA TURBIDITY IN THE KUNKEL TEST

Time, hr.	Untreated (10 dogs)	Treated (10 dogs)
0	2.40	2.30
3	2.53	2.12
5	2.68	2.12
7	2.62	1.72

These results seem to be related to a previous physiological study effected on adrenosterone.[9] Detailed results of physiological tests will be published elsewhere.

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(2) French Patent 1,085,464 (27-6-53); Belgian Patent 554,136 (French priority 13-1-56).

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