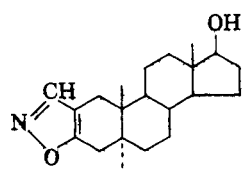
Communications TO THE EDITOR

Steroidal[2,3-d]isoxazoles

Sir:

We have previously reported[1] the effect on endocrinological activity produced by the fusion of a pyrazole ring to the 2,3-positions of several hormonally active steroids. Noteworthy changes in the type of endocrinological activity, or in the separation of several activities, are also observed when an isoxazole ring is similarly fused to hormonally active steroids. The resultant steroidal[2,3-d]-



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isoxazoles, (*e.g.*, I) constitute a new[2] class of modified steroids.

The reaction of 2-hydroxymethyleneandrostan-17β-ol-3-one[3] with hydroxylamine hydrochloride in ethanolic solution gave 17β-hydroxyandrostano-[2,3-d]isoxazole, I, m.p. 179.8–182.0°, $[\alpha]_D$ + 61.6°, λ_{max} 228 mμ (4900) (found: C, 75.93; H, 9.38; O, 9.90[4]). Treatment of I with cyclohexylpropionic anhydride in pyridine solution gave 17β-(3-cyclohexylpropionoxy)androstano[2,3-d]isoxazole, II, m.p. 140.4–141.8°, $[\alpha]_D$ + 40.6° (Found: C, 76.54; H, 9.63; N, 3.12).

Similarly, the reaction of hydroxylamine hydrochloride with the intermediate 2-hydroxymethylene-3-ketosteroids[1,5] gave 17β-hydroxy-17α-methylandrostano[2,3-d]isoxazole, III, m.p. 171.4–173.2°, $[\alpha]_D$ + 36.2° (found: C, 76.70; H, 9.55: O, 10.00), 17β-hydroxy-17α-methylandrost-4-eno[2,3-d]isoxazole, IV, m.p. 175.0–179.2°, $[\alpha]_D$ + 107.5°, λ_{max} 285 mμ (11,900) (found: C, 76.90; H, 8.77; O, 9.80), and 17β-hydroxy-17α-methylandrosta-4,6-dieno[2,3-d]isoxazole, V, m.p. 193.4–199.0°, $[\alpha]_D$ −187.8°, λ_{max} 245, 253, 319 mμ (3000, 2500, 19,800 respectively) (found: C, 77.19; H, 8.29; O, 10.05). From 2-hydroxymethylene-17α-methyl-19-norandrost-4-en-17β-ol-3-one[6] there was obtained the corresponding 17β-hydroxy-17α-methyl-19-norandrost-4-eno[2,3-d]isoxazole, VI, m.p. 160.2–161.0°, $[\alpha]_D$ − 43.3°, λ_{max} 287 mμ (10,400) (found: C, 76.78; H, 8.65; N, 4.51).

Compounds I, III, and IV proved to be very active when tested for myotrophic[7] and anabolic activities, and in addition they have low androgenic activity. Compound V, however, is a considerably less active myotrophic agent (and less androgenic) than either III or IV. In contrast to the corresponding steroidal[3,2-c]pyrazoles,[1] neither IV nor V show any estrogenicity.

Compound II is a very potent anabolic agent, with a long duration of action and minimal androgenicity. Peak response to this ester occurs from three to four weeks after a single subcutaneous injection.

Compound VI is progestational (equal in activity to progesterone intramuscularly, and at least as active as Ethisterone when given orally), highly active both anabolically and myotrophically, and in addition has a low degree of androgenic and estrogenic activities. The latter response, however, is atypical since considerable mucification and leucocytic infiltration accompany cornifying effects on the vaginal epithelium.

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(1) R. O. Clinton, A. J. Manson, F. W. Stonner, A. L. Beyler, G. O. Potts, and A. Arnold, *J. Am. Chem. Soc.*, 81, 1513 (1959).

(2) F. Winternitz, C. Menou, and E. Arnal, *Bull. soc. chim. France*, 505 (1960), have recently prepared 2α-cyanocholestan-3-one *via* the intermediate cholestano-[2,3-d]isoxazole; the latter compound was not isolated.

(3) J. Edwards and H. J. Ringold, *J. Am. Chem. Soc.*, 81, 5262 (1959). The compound described as 2-hydroxymethylenedrostan-17β-ol-3-one by F. L. Weisenborn and H. E. Applegate, *J. Am. Chem. Soc.*, 81, 1960 (1959) is actually the corresponding enol ether, 2-methoxymethyleneandrostan-17β-ol-3-one (data to be published from these laboratories).

(4) Melting points are corrected; rotations were taken in chloroform solution and ultraviolet spectra in 95% ethanol.

(5) H. J. Ringold, E. Batres, O. Halpern, and E. Necoechea, *J. Am. Chem. Soc.*, 81, 427 (1959).

(6) J. Edwards and H. J. Ringold, ref. 3.

(7) Anabolic activity was determined by nitrogen retention, myotrophic activity by the growth response of the levator ani muscle, androgenicity by the gain in weight of the ventral prostate, and estrogenicity by vaginal cornification, all in rats. Progestational activity was evaluated by the Clauberg test in rabbits. Compounds I and II were administered by subcutaneous injection and compounds III, IV, and V were given orally.