bon–carbon bond cleavage to ethyl 1-methylcyclopropanecarboxylate, which then is reduced to the observed product

DEPARTMENT OF CHEMISTRY KENNETH B. WIBERG
UNIVERSITY OF WASHINGTON
SEATTLE 5, WASHINGTON RICHARD P. CIULA

RECEIVED AUGUST 10, 1959

STEROIDS. CXXXII.[1] 2-FLUORO AND 21,21-DIFLUORO STEROIDS

Sir:

The fluorination of active methylene compounds with perchloryl fluoride has been demonstrated recently.[2] Subsequently, Gabbard and Jensen[3] utilized this reagent in the steroid series, preparing 2α-fluorocholestanone from cholestanone pyrrolidyl enamine while Kissman, Small and Weiss[4] prepared 2α-fluorohydrocortisone from 2-methoxalylhydrocortisone 20-ketal.

We have prepared a number of 2α-fluoro steroids in the potentially important androstane series by reaction of the sodio salt of the appropriate 2-hydroxymethylene-3-keto steroid with perchloryl fluoride followed by alkaline cleavage of the resultant 2-aldehydo-2-fluoro compounds.[5] Thus, 2-hydroxymethylene-testosterone,[6] -androstan-17β-ol-3-one (m.p. 125–130°, $[\alpha]$D + 60° (all rot. in $CHCl_3$), λ_{max}^{EtOH} 282 mμ, log ϵ 3.94), -17α-methyltestosterone,[7] and 2-hydroxymethylene-17α-methylandrostan-17β-ol-3-one,[7] in benzene solution, were reacted successively with sodium methoxide and perchloryl fluoride. Treatment of the reaction products with potassium acetate in boiling methanol gave 2α-fluorotestosterone (I) (m.p. 140–141°, $[\alpha]$D + 131°, λ_{max}^{EtOH} 242 mμ, log ϵ 4.15, λ_{max}^{KBr} 5.90 μ. Found for $C_{19}H_{27}FO_2$: C, 74.27; H, 8.85; F, 5.97); 2α-fluoroandrostan-17β-ol-3-one[8] (II) (m.p. 183–185°, $[\alpha]$D + 63°, λ_{max}^{EtOH} 283 mμ, log ϵ 1.44, λ_{max}^{KBr} 5.75 μ. Found for $C_{21}H_{31}FO_3.C_3H_6O$: C, 70.96; H, 8.91; F, 4.81); II acetate (m.p. 190–193°, $[\alpha]$D + 56°); 2α-fluoro-17α-methyltestosterone (III) (m.p. 168–169°, $[\alpha]$D + 116°, λ_{max}^{EtOH} 242 mμ, log ϵ 4.22, λ_{max}^{KBr} 5.90 μ. Found for $C_{20}H_{29}FO_2$: C, 75.30; H, 8.63; F, 5.80); 2α-fluoro-17α-methylandrostan-17β-ol-3-one (IV) (m.p. 193–194°, $[\alpha]$D + 46°, λ_{max}^{EtOH} 283 mμ, log ϵ 1.52, λ_{max}^{KBr} 5.75 μ. Found for $C_{20}H_{31}FO_2$: C, 74.49; H, 9.69; F, 5.89). The assignment of the 2α-fluoro configuration rests on the shift in the infrared and lack of shift in the ultraviolet of the carbonyl maximum[9] as well as on rotatory dispersion data.[10]

2α-Fluoro-17α-ethynyltestosterone (V) (m.p. 243–245°, $[\alpha]$D + 65°, λ_{max} 242 mμ, log ϵ 4.28, λ_{max}^{KBr} 3.00, 5.90 μ. Found for $C_{21}H_{27}FO_2$: C, 76.47; H, 8.28; F, 5.39) was prepared by condensing 17α-ethynyltestosterone with ethyl formate and treating the crude 2-hydroxymethylene compound as described above.

Since sodio malonic ester is difluorinated by perchloryl fluoride even in the absence of excess base[2] it appeared that 21,21-difluorination, leading to a hitherto unknown class of steroids, would be feasible. The sodio salt of 21-ethoxalyl-Δ^5-pregnen-3β-ol-20-one[11] in absolute ethanol or benzene and in the presence of excess sodium methoxide was treated with perchloryl fluoride and then methanolic potassium acetate yielding 21,21-difluoro-Δ^5-pregnen-3β-ol-20-one (m.p. 133–135°, $[\alpha]$D + 54°, λ_{max}^{KBr} 5.75 μ. Found for $C_{21}H_{30}F_2O_2$: C, 71.05; H, 8.88; F, 10.28). Oppenauer oxidation gave 21,21-difluoroprogesterone (VI) (m.p. 140–143°, $[\alpha]$D + 204°, λ_{max}^{EtOH} 241 mμ, log ϵ 4.22, λ_{max}^{KBr} 5.75, 6.00 μ. Found for $C_{21}H_{28}F_2O_2$: C, 72.54; H, 8.10; F, 10.14).

In preliminary seven day assays[12] in the castrate rat, I and II exhibited 20% and 50% of the androgenic potency of testosterone with myotrophic activity about 50% of the standard while compound III, orally administered in the same assay was 25% as androgenic as methyltestosterone. Both I and II were potent gonadotrophin inhibitors in a 10-day parabiotic rat assay.[12] VI was considerably less active than progesterone in the Clauberg assay[12] in sharp contrast to the activity of 21-monofluoroprogesterone.[13]

(1) Steroids CXXXI, J. Zderic and D. Chávez Limón, THIS JOURNAL, in press (1959).

(2) C. E. Inman, E. A. Tyczkowski, R. E. Oesterling and F. L. Scott, *Experientia*, **14**, 355 (1958); C. E. Inman, R. E. Oesterling and E. A. Tyczkowski, THIS JOURNAL, **80**, 6533 (1958).

(3) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958).

(4) H. Kissman, A. M. Small and M. J. Weiss, THIS JOURNAL, **81**, 1262 (1959).

(5) A number of the fluoro hormone analogs reported in this paper have been prepared by E. V. Jensen and co-workers through alternate routes. Their results are published simultaneously p. 5259.

(6) F. Weisenborn, D. Remy and T. L. Jacobs, THIS JOURNAL, **76**, 552 (1954).

(7) H. J. Ringold, E. Batres, O. Halpern and E. Necoechea, *ibid.*, **81**, 427 (1959).

(8) Dr. E. V. Jensen kindly compared our product with samples prepared through the enamine and enol ether (see ref. 5) routes and found them to be identical.

(9) R. N. Jones, D. A. Ramsey, F. Herling and K. Dobriner, THIS JOURNAL, **74**, 2828 (1952); B. Ellis and V. Petrow, *J. Chem. Soc.*, 1179 (1956). See also ref. 2 and 3.

(10) C. Djerassi, I. Fornaguera and O. Mancera, THIS JOURNAL, **81**, 2383 (1959).

(11) H. Ruschig, *Ber.*, **88**, 878 (1955).

(12) Assays by The Endocrine Laboratories, Madison, Wisconsin.

(13) P. Tannhauser, R. J. Pratt and E. V. Jensen, THIS JOURNAL, **78**, 2658 (1956).

RESEARCH LABORATORIES
SYNTEX, S. A. J. EDWARDS
APDO. POSTAL 2679 H. J. RINGOLD
MÉXICO, D. F.

RECEIVED JULY 20, 1959

ISOTOPE SEPARATION BY ION EXCHANGE

Sir:

The sign, magnitude and trend of the separation factors observed by Lee and Begun[1] provide another example of the close analogy between ion exchange resins and concentrated aqueous solution, because the observed values are very nearly those which would be expected from an equilibrium between a dilute aqueous solution and a concentrated aqueous solution of a molality corresponding to that of the exchangers concerned.

For two aqueous solutions, *e.g.*, of LiCl, the separation factor $k = 1 + \epsilon$ is given by the ratio of

(1) D. A. Lee and G. M. Begun, THIS JOURNAL, **81**, 2332 (1959).