frared analyses were obtained through the courtesy of the Institute for Atomic Research.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA

HENRY GILMAN
ERNEST A. ZUECH

Received July 6, 1959

Adrenal Hormones and Related Compounds. VI.[1] A Series of 2-Fluorotestosterone Derivatives

Sir:

Diminution or elimination of androgenic activity without loss of other properties exhibited by "androgens" is a major objective in the modification of C-19-steroids. Partial success has been achieved in the preparation of the preferentially anabolic agents 9α-fluoro-11β-hydroxy-17-methyltestosterone (Halotestin),[2] 19-nortestosterone and its esters,[3] and 17-ethyl-19-nortestosterone,[4] and in the recent findings that Halotestin[5] and 2-methylandrostanolone[6] are of particular value in the treatment of mammary carcinoma.

Since the introduction of perchloryl fluoride and the development of techniques for its use in the fluorination of carbanions,[7] a number of α-fluoro ketosteroids have been prepared.[8] We now wish to report the synthesis of some 2-fluoro derivatives in the testosterone series.

When testosterone, 17-methyltestosterone, 9(11)-dehydro-17-methyltestosterone,[2] 11β-hydroxy-17-methyltestosterone,[2] and 9α-fluoro-11β-hydroxy-17-methyltestosterone[2] were condensed with ethyl oxalate using sodium methoxide in *t*-butyl alcohol,[1] the sodium enolates of the resulting 2-glyoxylates were obtained. These salts were treated with perchloryl fluoride in methanol and afforded, after basic cleavage of the ethoxyoxalyl residues, the corresponding 2-fluoro derivatives (see Table I). While 2,9-difluoro-11β-hydroxy-17-methyltestosterone was thus obtained in quite low yield it could be readily prepared from 2-fluoro-9(11)-dehydro-17-methyltestosterone *via* the opening of its 9,11β-epoxide with hydrogen fluoride.

TABLE I

9α-X- 11β-Y- 17α-Z- 2-FLUOROTESTOSTERONES

X	Y	Z	M.P., °C.	Yield, %	Anal., Found, % C	H	F
H	H	H	159.5–161	70	74.54	9.12	5.91
H	H	CH_3	174–174.5	42	75.17	9.53	6.10
H	OH	CH_3	217–220	60	71.79	8.51	5.6
F	OH	CH_3	228 (dec.)	8	68.08	8.29	9.67
$\Delta^{9(11)}$		CH_3	182–182.5	53	75.27	8.95	5.96

While many androgens have been reported to inhibit the mammary fibroadenoma in the rat,[9] 2-fluorotestosterone was found to effect nearly 100% inhibition of the mammary fibroadenoma which had become resistant to the action of testosterone propionate.[10] Even at elevated doses, 2-fluorotestosterone exhibited no indication of androgenic activity[11] yet, in the female rat, marked increases in body weight were observed.[12]

RESEARCH LABORATORIES
THE UPJOHN COMPANY
KALAMAZOO, MICH.

ALAN H. NATHAN
JOHN C. BABCOCK
JOHN A. HOGG

Received July 24, 1959

(1) Paper V in this series: A. H. Nathan, B. J. Magerlein, and J. A. Hogg, *J. Am. Chem. Soc.*, in press.

(2) M. E. Herr, J. A. Hogg, and R. H. Levin, *J. Am. Chem. Soc.*, **78**, 500 (1956).

(3) U. S. Patent **2,798,879**; R. O. Stafford, B. J. Bowman, and K. J. Olsen, *Proc. Soc. Exptl. Biol. Med.*, **86**, 322 (1954).

(4) F. B. Colton, L. N. Nysted, B. Riegel, and A. L. Raymond, *J. Am. Chem. Soc.*, **79**, 1123 (1957); F. J. Saunders and V. A. Drill, *Endocrinology*, **58**, 567 (1959).

(5) B. J. Kennedy, *Cancer*, **10**, 813 (1957).

(6) H. J. Ringold and G. Rosenkranz, *J. Org. Chem.*, **21**, 1333 (1956); C. M. Blackburn and D. S. Childs, Jr., *Proc. Staff Meetings Mayo Clinic*, **34**, 113 (1959).

(7) 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, *J. Am. Chem. Soc.*, **80**, 6533 (1958).

(8) (a) R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958); (b) H. M. Kissman, A. M. Small, and M. J. Weiss, *J. Am. Chem. Soc.*, **81**, 1262 (1959).

(9) C. Huggins, Y. Torralba, K. Mainzer, *J. Exptl. Med.*, **104**, 525 (1956); E. M. Glenn, S. L. Richardson, and B. J. Bowman, *Endocrinology*, **64**, 379 (1959); E. M. Glenn, S. L. Richardson, S. C. Lyster, and B. J. Bowman, *Endocrinology*, **64**, 390 (1959).

(10) Private communication from Dr. E. M. Glenn.

(11) L. E. Barnes, R. O. Stafford, M. E. Guild, L. C. Thole and K. J. Olson, *Endocrinology*, **55**, 77 (1954).

(12) We wish to thank Drs. E. M. Glenn and W. E. Dulin and S. L. Richardson, S. C. Lyster, and B. J. Bowman of our Department of Endocrinology for the biological data summarized above.

Preparation and Some Reactions of Allyllithium

Sir:

Recent mention[1] that allyllithium has found use in the U.S.S.R. as a catalyst for stereospecific polymerization of dienes prompts this report of our new synthesis of allyllithium and methallyllithium by the exchange reaction between organolithium reagents and allyl- and methallyl-tin compounds.[2] Allyllithium was prepared first[3] by reaction of allylmagnesium bromide and lithium. However, the resulting solution of allyllithium was contaminated

(1) *Chem. Eng. News*, **37**, No. 27, 41 (1959).

(2) A similar reaction was used to prepare vinyllithium for the first time: D. Seyferth and M. A. Weiner, *Chem. & Ind. (London)*, **1959**, 402.

(3) T. E. Londergan, U. S. Patent **2,734,091** (1956).