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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]

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(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).

with allylmagnesium bromide, allyl bromide, biallyl and lithium bromide, whereas our method gives much purer allyllithium solutions. A few examples may serve to illustrate our method.

Phenyllithium (0.127 mole) in ether was added to 0.127 mole of allyltriphenyltin in ether, and the mixture was stirred under nitrogen for 30 min. Tetraphenyltin precipitated immediately. 4-Methyl-2-pentanone (0.12 mole) was added and the mixture refluxed for 1.5 hr. Hydrolysis, filtration of tetraphenyltin (53.8 g., 99%), and distillation of the organic layer gave 11.1 g. (65%) of 4,6-dimethyl-1-hepten-4-ol, b.p. 70–71° at 20 mm., n_D^{20} 1.4400 (reported[4] n_D^{20} 1.4402). In a similar manner, allyllithium was used to prepare allyltriphenylsilane (74% from triphenylchlorosilane; 60% from triphenylsilane), allyltriphenylgermane (54% from triphenylbromogermane), allyltri-*n*-butyltin (69% from tri-*n*-butyltin chloride), and octene-1 (52% from *n*-amyl iodide). Carbonation gave vinylacetic acid in 25% yield. Allyllithium is fairly stable in ether solution. Addition of tri-*n*-butyltin chloride to an allyllithium solution 20 hr. after its preparation resulted in a 69% yield of allyltri-*n*-butyltin.

Allyltri-*n*-butyltin serves equally well in the preparation of allyllithium. To 0.098 mole of allyltri-*n*-butyltin was added 0.098 mole of phenyllithium in ether. After 1 hr., 0.09 mole of 4-methyl-2-pentanone was added. Hydrolysis and distillation of the organic layer gave 4,6-dimethyl-1-hepten-4-ol and tri-*n*-butylphenyltin in 70 and 78% yields, respectively. This shows that the driving force of the exchange reaction is not the formation of an insoluble tin compound. The reaction of tetraallyltin with phenyllithium may be used to prepare allyllithium in pentane solution; the reagent so prepared was used to convert tri-*n*-butyltin chloride to allyltri-*n*-butyltin in 65% yield.

Methallyllithium in ether was prepared similarly from phenyllithium and methallyltriphenyltin. This reagent was used to obtain 2-methyl-1-penten-4-ol (59%) from acetaldehyde and triethylmethallylsilane (68%) from triethylbromosilane.

A detailed description of these experiments as well as of related work will be given at a later date.

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