

2 were prepared because of their potential as irreversible progesterone antagonists. The  $13\beta,16\beta$  bridge was constructed by intramolecular alkylation of the C-16 enolate anion from 3-methoxy- $13\beta$ -(3'-tosyloxypropyl)gon-3,5-dien-17-one, the latter being obtained *via* Birch reduction of both aryl groups of 1. The  $11\beta,13\beta$  bridge was constructed by Prins cyclization of  $17\beta$ -acetoxy-3-methoxy- $13\beta$ -(3'-oxopropyl)gon-1,3,5(10),9(11)-tetraene (3), itself obtained *via* Birch reduction of only the side chain aryl group of 1. The *in vitro* binding affinities of  $11\beta,13\beta$ - and  $13\beta,16\beta$ -propano derivatives of  $17\alpha$ -ethynyl- $17\beta$ -hydroxygon-4-en-3-one for the cytosolic receptor protein were 22% and 1.3%, relative to progesterone.

#### 7. Conjugate addition of organocopper reagents to steroidal polyenones

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Introduction of a  $7\alpha$ -methyl function and a  $\Delta^{14}$ -double bond into 19-nortestosterone enhances androgenic activity to  $1000 \times$  testosterone in the chick comb assay.  $7\alpha$ -Methyl-14-dehydro-19-nortestosterone was prepared from  $7\alpha$ -methyltestosterone which in turn was obtained from dehydroisandrosterone. An early step in the synthesis involves conjugate addition of copper-catalyzed methyl Grignard reagent to  $17\beta$ -ethylenedioxyandrosta-4,6-diene-3,17-dione, resulting in a mixture of  $7\alpha$ - and  $7\beta$ -methyl isomers in the ratio of 2:1; separation of the  $7\alpha$ -isomer is laborious. In contrast, conjugate addition of lithium dimethylcuprate to  $17\beta$ -acetoxyestra-4,6-dien-3-one, a 19-norsteroid, yields only the  $7\alpha$ -methyl adduct. In this light one would also expect  $17\beta$ -acetoxyestra-4,6,14-triene to undergo "normal" conjugate addition to form a  $7\alpha$ -methyl adduct. Contrary to expectation, the conjugate addition yielded the  $7\beta$ -methyl adduct *exclusively*. The steric factors responsible for the  $7\beta$ -methyl adduct from a  $\Delta^{14}$ -steroid can be explained by X-ray crystal data obtained on a variety of  $\Delta^{14}$ -steroids.

#### 8. Identification of natural spirolactones in man

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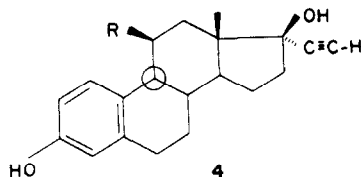
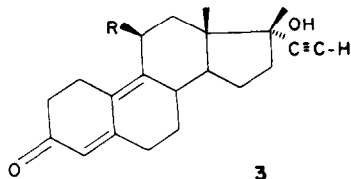
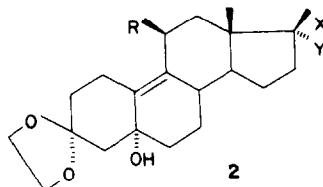
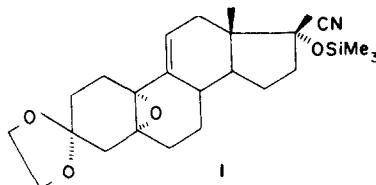
The extract of a urinary pool of normal man without treatment was analysed by Gas Liquid Chromatography (GLC) with electron capture detection using an OV<sub>17</sub> 3<sup>m</sup>—6 feet column. The chromatogram shows two peaks with a retention time ( $R_T$ ) of 26.4 and 41.2 min. respectively. The <sup>1</sup>H and <sup>13</sup>C n.m.r. spectra of the purified compound with  $R_T$  value of 41.2 indicates a steroid molecule with a spirolactonic structure similar to that of Spirolactone or Canrenone, and with two O-atoms localized on carbon 6 and 7 respectively as an hydroxyl group or as a methoxy group. Mass spectrometry of this compound confirms the n.m.r. data. Finally the preliminary results also indicate a spirolactonic structure for the compound with  $R_T$  of 26.4 min

#### 9. Regional- and stereo-specific synthesis of $11\beta$ -substituted 19-nor-steroids

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Treatment of  $5\alpha,10\alpha$ -epoxy  $\Delta^9(11)$ -steroids with lithium organocuprates or copper I catalyzed Grignard reagents, leads to exclusive  $11\beta$ -substitution (1  $\rightarrow$  2). Dehydration of

the intermediate allylic alcohol and simultaneous unmasking of the 3-keto function affords the novel  $11\beta$  alkyl, alkenyl or aryl 3-keto- $\Delta^{4,9}$  dienones (3) which can be further transformed by known procedures to the corresponding ring A aromatic steroids (4). The mechanism of  $11\beta$ -alkylation will be discussed. Cytosolic receptor affinities will be briefly presented.



(a) X = CN  
Y = OSiMe<sub>3</sub>

(b) X = OH  
Y = C≡C-H

#### 10. Sultine analogues of spirolactones

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New structural analogues of the antimineralocorticoid spirolactones, where the carbonyl group of the  $17\beta$  lactonic ring has been replaced by a sulphanyl group, have been synthesised from  $17,20$ -epoxysteroids.

The resulting spirosultines (1) and (2), each of which existing in two diastereoisomeric forms, have been studied systematically *in vitro* for their ability to bind to hormonal receptors and *in vivo* for their aldosterone antagonising properties in rats. All spirosultines of type (1) bind moderately to mineralocorticoid receptors. As in spirolactone series diuretic potencies and hormonal side effects depend largely on the nature of the substituents in different pos-