

1. CHEMISTRY

1. Chemical and pharmacological studies on steroidal saponins isolated from *Trigonella foenum graecum*

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Five new steroidal saponins named as B, C, D, E and G have been isolated from an ethanolic extract of leaves of *Trigonella foenum graecum*. Three of these saponins have been found to possess diosgenin as aglycone and different sugars in different molar ratio. Some pharmacological activities of the saponins B, C, D and the mixture of all five saponins (named as A) were assessed. Substances A and D produced a marked increase in rat blood pressure at 1 mg dose while B and C did not produce any significant effect at this dose. However, all the compounds produced cardiotonic activity when tested using frog's heart perfusion *in situ*.

2. A novel approach for the total synthesis of 12-thiaequilenin and its 3-deoxy analogue

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This communication constitutes the very first report on a new approach towards the total synthesis of the hitherto unknown 12-thiasteroids mentioned above. The starting materials, 6-methoxy-1-mercaptomethylnaphthalene (I) and 1-mercaptomethylnaphthalene (II) are converted into the corresponding lead mercaptides (III & IV) in high yields. These lead salts (III & IV) on treatment with *N*-bromosuccinimide (NBS) afforded *N*-(6-methoxy-1-mercaptomethylnaphthyl) succinimide and *N*-(1-mercaptomethylnaphthyl) succinimide (V & VI) which on treatment with 2-methyl-1,3-cyclopentanedione gave the anticipated 3-methoxy-12-thia-8,14-seco-1,3,5(10),6,8-estrapentaene-14,17-dione (VII) and 12-thia-8,14-seco-1,3,5(10),6,8-estrapentaene-14,17-dione (VIII) in 70% yield. Cyclodehydration of VII & VIII to furnish the above mentioned 12-thiasteroids is in progress.

3. 7a-Aza-B-homo[7a,7-d]tetrazole analogues of progesterone and testosterone

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We have synthesised 7a-aza-B-homo[7a,7-d]tetrazole analogues of progesterone and testosterone, which are worthy of biological testing. (25R)-7a-Aza-B-homo-5-spirosten-7a,7-d]tetrazol-3 β -yl acetate, prepared from (25R)-7-oxo-5-spirosten-3 β -yl acetate by the Schmidt reaction, gave on Marker degradation 20-oxo-7a-aza-B-homo-5,16-pregnadieno[7a,7-d]tetrazol-3 β -yl acetate. The latter on partial hydrogenation over Pd-BaSO₄, followed by hydrolysis and Oppenauer oxidation gave 7a-aza-B-homo-4-pregneno[7a,7-d]tetrazole-3,20-dione. 7a-Aza-B-homo-5-androsteno[7a,7-d]tetrazole-3 β ,17 β -diol diacetate was prepared from 5-androstene-3 β ,17 β -diol diacetate. The tetrazolosteroid was partially hydrolysed. The product on Oppenauer oxidation gave 3-oxo-7a-aza-B-homo-4-androsteno[7a,7-d]tetrazol-17 β -yl acetate.

4. Synthesis and examination of new 17-spiro-steroids

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During the search for aldosterone-blocking steroids we examined the possibilities of synthesizing new types of steroid-spiro-heterocycles. Spiro-oxiranes, prepared from 17-keto-steroids were used as starting materials. These were transformed with aliphatic primary amines into 17 α -alkylamino-methyl-17 β -hydroxy-steroids, from which thiourea derivatives were prepared. Using the ring closure reactions of the latter, spiro-imino-oxazolidines and thiooxazolidines, as well as spiro-1,2,4-oxathiazines (representing a new heterocyclic ring system), were synthesized. All structures were confirmed by chemical and physical methods. Certain biological data and chemical transformations of these compounds turned our attention to the steroid-spiro-oxazolidinones. Several methods were developed for the synthesis of this earlier, scarcely investigated, class of compounds. The aldosterone-blocking effect of some of the new steroid-spiro-oxazolidinone derivatives equals that of Spironolactone, while others possess remarkable antian-drogen character.

5. Synthesis and activity (post-coital antifertility and hormonal) of 2,7 α -dimethyl steroids

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Certain 7 α -methyl steroids possess post-coital antifertility activity in the hamster when administered on days 3-8 of pregnancy. Detailed examination of the effect of further substitution on the activity of these compounds was therefore initiated. 2 α - and 2 β -methyl substituents were introduced by alkylation of 7 α -methyltestosterone followed by rearrangement of the double bond to the 5-ene-position and reduction to the 3 α - and 3 β -alcohols. 2,7 α -dimethylestrane analogs were obtained by conjugate addition to 2-methylestra-4,6-dien-3-ones followed by reduction. Stereochemical assignments were made by n.m.r. studies of the various isomers. 2,7 α -dimethylandrostanes having a 4-ene-3-one moiety were potent androgenic compounds. Conversion to the 5-ene-3 β -ols essentially eliminated androgenic activity. The resulting compounds were potent post-coital antifertility agents. However, they exhibited somewhat surprising uterotrophic activity and had significant affinity for uterine estrogen receptor. Since 2-substituents have such important influence on the modulation of hormonal activities, further substitution in this position is under study.

6. The synthesis of 11 β ,13 β - and 13 β ,16 β -propano steroids: probes of hormonal activity

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As a continuation of our studies directed towards the synthesis of modified steroids with improved antifertility activity, we have synthesized 3-methoxy-13 β -(3'-phenoxypropyl)-1,3,5(10)-trien-17 β -ol (1) and 17 α -ethynyl-17 β -hydroxy-13 β -(3'-hydroxypropyl)gon-4-en (2). Several derivatives of

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- 13β -(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 17β -acetoxy-3-methoxy- 13β -(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 17α -ethynyl- 17β -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 7α -methyl function and a Δ^{14} -double bond into 19-nortestosterone enhances androgenic activity to $1000 \times$ testosterone in the chick comb assay. 7α -Methyl-14-dehydro-19-nortestosterone was prepared from 7α -methyltestosterone which in turn was obtained from dehydroisandrosterone. An early step in the synthesis involves conjugate addition of copper-catalyzed methyl Grignard reagent to 17β -ethylenedioxyandrosta-4,6-diene-3,17-dione, resulting in a mixture of 7α - and 7β -methyl isomers in the ratio of 2:1; separation of the 7α -isomer is laborious. In contrast, conjugate addition of lithium dimethylcuprate to 17β -acetoxyestra-4,6-dien-3-one, a 19-norsteroid, yields only the 7α -methyl adduct. In this light one would also expect 17β -acetoxyestra-4,6,14-triene to undergo "normal" conjugate addition to form a 7α -methyl adduct. Contrary to expectation, the conjugate addition yielded the 7β -methyl adduct *exclusively*. The steric factors responsible for the 7β -methyl adduct from a Δ^{14} -steroid can be explained by X-ray crystal data obtained on a variety of Δ^{14} -steroids.

8. Identification of natural spirolactones in man

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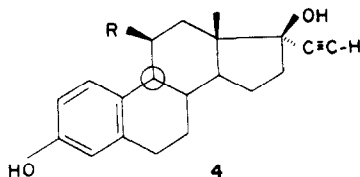
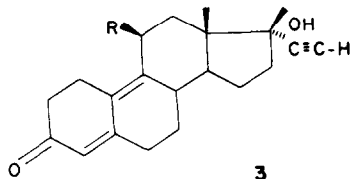
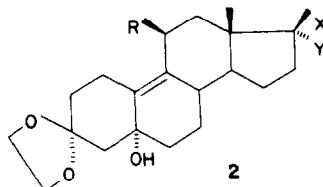
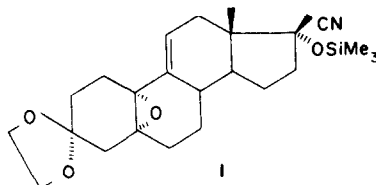
The extract of a urinary pool of normal man without treatment was analysed by Gas Liquid Chromatography (GLC) with electron capture detection using an OV₁₇ 3^m—6 feet column. The chromatogram shows two peaks with a retention time (R_T) of 26.4 and 41.2 min. respectively. The ^1H and ^{13}C n.m.r. spectra 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 11β -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 11β -substitution ($1 \rightarrow 2$). Dehydration of

the intermediate allylic alcohol and simultaneous unmasking of the 3-keto function affords the novel 11β 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 11β -alkylation will be discussed. Cytosolic receptor affinities will be briefly presented.



(a) X = CN
Y = OSiMe₃

(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 17β 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-