0,5–10 mg/kg i.m., Noradrenalin und Adrenalin und Isoprenalin in der Dosis von 0,5 mg/kg i.m. den Serumspiegel der freien Fettsäuren an der gesättigten Ratte erhöht (Tabelle II). Diese Wirkung war bei Isoprenalin, Noradrenalin und bei Adrenalin stärker als bei den anderen Substanzen. Die Wirkung der adrenergischen Stimulatoren auf die freien Fettsäuren der Ratte wird durch eine Vorbehandlung mit dem β-Adrenolytikum Kö 592 (10 mg/kg i.m., 5 min vor den adrenergisch stimulierenden Substanzen) in folgender wachsender Aktivitätsreihenfolge antagonisiert: Noradrenalin, Adrenalin, Isoprenalin, Metaproterenol (Tabelle II).

Diskussion. Die neuen β-adrenergischen Substanzen stimulierenden Typs (Terbutalin, Soterenol, Salbutamol und Quinterenol) zeigen neben bedeutenden tracheobronchodilatatorischen Eigenschaften[1–4], die mit leichten Nebenwirkungen auf das Herz verbunden sind, auch mässige hyperglykämisierende Wirkungen an der Ratte, die nur in hohen Dosen im Fall von Soterenol und von Salbutamol an ein Anwachsen der freien Fettsäuren des Serums assoziiert sind; diese adrenergischen Wirkungen sind vom Typ β, da sie durch eine Vorbehandlung mit einem β-Adrenolytikum, dem Kö 592, antagonisiert werden.

Wegen ihrer geringen Wirkungen auf den Glukose- und Lipidstoffwechsel sowie auf die Herzgefässe[1–4] haben Terbutalin, Soterenol, Salbutamol, Quinterenol und auch Metaproterenol eine starke Wirkung auf die adrenergischen Rezeptoren vom Typ β-2 und eine schwache Wirkung auf adrenergische Rezeptoren vom Typ β-1, entsprechend der Unterteilung, die LANDS et al.[9] vorschlugen.

Die hyperglykämisierende Wirkung, die wir mit dem β-Adrenolytikum Kö 592 notierten, bestätigt Beobachtungen von ENGELHARDT[10].

Summary. Actions of various adrenergic drugs (adrenaline, noradrenaline, isoprenaline, metaproterenol, terbutaline, salbutamol, soterenol, quinterenol, chlorprenaline) on the glycemia and on free fatty acids of the rat have been described.

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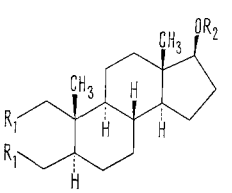
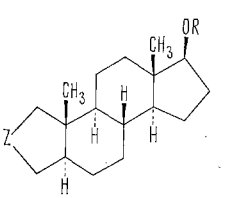
Preparation and Androgenic Activity of Novel Heterocyclic Steroids

We wish to describe the preparation of oxa, selena-, tellurio and related steroids as probes of steroid structural requirements. We have been interested in the reasons for the importance for androgenic activity of sp^2 atoms at C-2 and/or C-3 of steroids[1,2]. This could be due to the steric characteristics of the sp^2 center, to the electronic nature of such atoms, or, jointly, to both effects. The general problem of distinguishing between such alternatives has been reviewed by MAUTNER[3] who has used isosteric non-isoelectronic analogs to obtain information about forces within the drug-receptor complex[4]. It is noteworthy, in this connection, that the various structure-activity theories concerning androgens[5] ignore the effects of conformational transmission[6] and, therefore, consider the effects of a structural alteration to be restricted to the immediate vicinity of the modified grouping. The possibility that this is not the case can also be explored by the examination of isologous series[3].

Our recent finding[7] that 2-thia-A-nor-5α-androstan-17β-ol, prepared as an isostere of 17β-hydroxy-5α-androst-2-ene, is a potent androgen led us to examine the corresponding oxa- and selena-isologs. Reduction of diester **1**[7] ($LiAlH_4$) gave diol **2**, mp 202–205°[8] which on heating in DMSO[9] afforded cyclic ether **4**, mp 140–143°. Treatment of dibromide **3**, with sodium selenide[10] gave selenasteroid **7**, mp 157–159°; the tellurio-derivative **8**, mp 145–146° was obtained in analogous fashion by the action of sodium telluride[11] on **3**. Similarly, the disulfide **9**, mp 153–154° was prepared from **3** by reaction with sodium disulfide[12]. Oxidation of thiasteroid **6** ($NaIO_4$ in acetone-water) gave only α-sulfoxide **10**[13], mp 139–140° whereas the action of *m*-chloroperbenzoic acid on **6** gave sulfone **11**, mp 243–244°.

The data from the pharmacological testing[14,15] are displayed in the Table. Selena- and thiasteroids **7** and **5** have comparable activity but oxa-, sulfoxide and sulfone derivatives **4**, **10** and **11** are inactive. Therefore, thiasteroid **5** is almost certainly active as such, and not as its most likely sulfoxide and sulfone metabolites **10** and **11** respectively. The covalent radii[16] of selenium (1.17 Å) and sulfur (1.04 Å) are nearly the same, and larger than oxygen (0.66 Å), whereas the electron distribution in all of these heterocycles is different[17]. Therefore, the fact that selenasteroid **7** is active, whereas oxasteroid **4** is inactive, suggests that *steric*, and not *electronic* factors are involved in the C-2, C-3 structural requirements of androgens. Confirmation for this was provided by the activities





1	$R_1 = CO_2Me$,	$R_2 = Ac$	**4**	Z = O,	R = H
2	$R_1 = OH$,	$R_2 = H$	**5**	Z = S,	R = H
3	$R_1 = Br$,	$R_2 = Ac$	**6**	Z = S,	R = Ac
			7	Z = Se,	R = H
			8	Z = Te,	R = H
			9	Z = S–S,	R = Ac
			10	Z = α-SO,	R = Ac
			11	$Z = SO_2$,	R = Ac
			12	$Z = CH_2CH_2CO$,	R = H

Androgenic-myotrophic assay

Compound (total dose, mg)	Weight (mg)[a]			Body weight (g)	
	Ventral prostate	Seminal vesicle	Levator ani	Initial	Final
Castrate control	15.6 ± 0.41	11.8 ± 0.30	27.0 ± 1.35	55	94
Testosterone (0.3)	25.6 ± 2.47	15.1 ± 0.76	31.4 ± 2.50	55	96
Testosterone (0.6)	52.5 ± 3.48 $p<0.001$	21.8 ± 2.35 $p<0.01$	37.6 ± 1.89 $p<0.01$	55	97
4[b] (3.0)	23.3 ± 2.56 p NS[c]	13.0 ± 0.22 p NS	29.2 ± 2.36 p NS	57	89
5[d] (3.0)	61.9 ± 6.04 $p<0.001$	48.6 ± 3.56 $p<0.001$	65.2 ± 3.45 $p<0.001$	55	95
5 (0.6)	40.5 ± 5.28 $p<0.01$	16.3 ± 0.73 $p<0.01$	33.1 ± 4.30	–	–
7 (3.0)	84.6 ± 5.42 p 0.001	51.0 ± 1.42 p 0.001	72.7 ± 2.71 p 0.001	55	101
8[d] (3.0)	92.6 ± 7.56 $p<0.001$	59.4 ± 3.55 $p<0.001$	67.8 ± 2.73 $p<0.001$	54	92
8[d] (0.3)	23.6 ± 2.03 $p<0.05$	15.2 ± 1.51 $p<0.10$	34.7 ± 2.88 $p<0.05$	–	–
9[d] (3.0)	112.4 ± 3.34 $p<0.001$	79.1 ± 2.68 $p<0.001$	71.5 ± 3.90 $p<0.001$	55	102
10[b] (3.0)	17.4 ± 0.66 p NS	12.4 ± 0.16 p NS	30.0 ± 2.51 p NS	57	91
11[b] (3.0)	13.3 ± 0.81 p NS	12.4 ± 0.80 p NS	28.8 ± 1.99 p NS	57	91

[a] Mean ± S.E. [b] Data from a second experiment with similar control values. [c] Not significant at p 0.01. [d] Data from another experiment with similar control values.

of tellurio-steroid **8** which is somewhat more active than thiasteroid **5**, and especially by disulfide **9**, which is that most active compound in the series. The covalent radius of tellurium (1.37 Å) is considerably larger than that of sulfur. It is clear therefore, that an exact isostere of a vinyl group is not mandatory for activity, but that a somewhat larger substitution may be made. Indeed, even the enlargement of the ring by the insertion of *two* sulfur atoms is permissible, as in **9**. On the other hand, the 7-membered system A-homo-4-oxo-5α-androstan-17β-ol (12) is known to be inactive[18]. Our data indicate convincingly that an A-ring *equivalent in size to a six-membered or larger carbocyclic ring*, and having *atoms which flatten the ring in the vicinity of C-2 and C-3*, or their replacement, is important for androgenic activity. Electronic characteristics of the A-ring are of minor importance. These studies are being extended[19].

Zusammenfassung. Die Darstellung verschiedener A-Nor-5α-androstan-Verbindungen, die im A-Ring ein Schwefel-, Selen- oder Tellur-Atom haben, wird beschrieben. Sie besitzen, im Gegensatz zu den entsprechenden Oxa-Verbindungen, anabol-androgene Aktivität. 2,3-Dithia-5α-androstan-17β-ol-Acetat hatte ebenfalls hohe anabol-androgene Wirksamkeit. Daraus wird geschlossen, dass für die anabol-androgene Aktivität, nicht die elektronischen, sondern die sterischen Eigenschaften der C-2 und C-3 Atome, beziehungsweise ihre Substituenten, von Bedeutung sind.

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