[Chem. Pharm. Bull. 16(8)1456—1459(1968)]

UDC 547.92.09 : 615.217.5

Investigations on Steroids. IX.[1] Pharmacological Studies. (3). Myotrophic and Androgenic Activities of 17β-Hydroxy-5α-androstano-[2,3-*c*]furazan and Its Derivatives

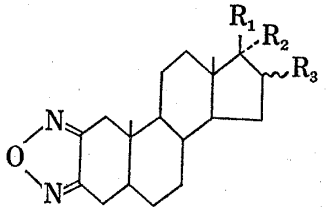
Akira Kasahara, Takeshi Onodera, Yasuo Oshima, and Masao Shimizu

Central Research Laboratory, Daiichi Seiyaku Co., Ltd.[2]

(Received August 21, 1967)

17β-Hydroxy-5α-androstano[2,3-*c*]furazan (I) has been shown to possess a high myotrophic activity and a low androgenic activity by subcutaneous injection, but its activities by oral route are very low. On the other hand, when given orally, 17-(2-tetrahydropyranyl) and 17-(1-cyclopentenyl)ethers of I are highly myotrophic and have shown a good separation of myotrophic and androgenic activities. The myotrophic and androgenic activities of 17α-ethyl, vinyl, ethynyl, 16-methylene, 16β-methyl, 16α-, and 16β-hydroxy derivatives of I are less than those of I.

In Part V[3] of this series, it was shown that 17β-hydroxy-17α-methyl-5α-androstano [2,3-*c*]furazan (furazabol[4]) is a potent anabolic steroid with low androgenicity. The biological interest in this compound led us to examine the activities of various steroidal furazans. The present paper concerns the correlation between the chemical modification in D-ring of 17β-hydroxy-5α-androstano[2,3-*c*]furazan and myotrophic-androgenic activity.



Compound	R_1	R_2	R_3
I	OH	H	H
II	R_1, R_2 : =O		H
III	-O- (2-tetrahydropyranyl)	H	H
IV	-O- (1-cyclopentenyl)	H	H
V	OH	$-C_2H_5$	H
VI	OH	$-CH=CH_2$	H
VII	OH	$-C\equiv CH$	H
VIII	OH	H	$=CH_2$
IX	OH	H	$-CH_3(\beta)$
X	OH	H	$OH(\alpha)$
XI	OH	H	$OH(\beta)$

Chart 1

Materials and Methods

The compounds (I to VII[6] and VIII to XI[7]) were synthesized in this laboratory. Testosterone propionate was purchased from the Tokyo Kasei Co., Ltd. and methyltestosterone from the Iwaki Seiyaku Co., Ltd. The compounds used in the present experiments are listed below. The chemical structures of these compounds are shown in Chart 1.

17β-Hydroxy-5α-androstano[2,3-*c*]furazan (I), mp 160—161°; 17-oxo-5α-androstano[2,3-*c*]furazan (II), mp 184—185°; 17β-hydroxy-5α-androstano[2,3-*c*]furazan 17-(2-tetrahydropyranyl)-ether (III), mp 109.5—113.5°; 17β-hydroxy-5α-androstano[2,3-*c*]furazan 17-(1-cyclopentenyl)ether (IV), mp 124—126°; 17α-ethyl-17β-hydroxy-5α-androstano[2,3-*c*]furazan (V), mp 143—144.5°; 17β-hydroxy-17α-vinyl-5α-androstano[2,3-*c*]furazan (VI), mp 177—178.5°; 17α-ethynyl-17β-hydroxy-5α-androstano[2,3-*c*]furazan (VII), mp 219—

1) Part VIII: *Chem. Pharm. Bull.* (Tokyo), **15**, 523 (1967).
2) Location: *Minamifunabori-cho, Edogawa-ku, Tokyo.*
3) A. Kasahara, T. Onodera, M. Mogi, Y. Oshima, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 1460 (1965).
4) Referred to as androfurazanol in previous communications.[3,5]
5) A. Kasahara, T. Onodera, H. Tachizawa, Y. Oshima, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **14**, 285 (1966).
6) G. Ohta, T. Takegoshi, K. Ueno, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), **13**, 1445 (1965).
7) K. Ueno and G. Ohta, *Chem. Pharm. Bull.* (Tokyo), **15**, 518 (1967).

220°; 17β-hydroxy-16-methylene-5α-androstano[2,3-*c*]furazan (VIII), mp 244—247°; 17β-hydroxy-16β-methyl-5α-androstano[2,3-*c*]furazan (IX), mp 261—263°; 16α,17β-dihydroxy-5α-androstano[2,3-*c*]furazan (X), mp 222—224°; 16β,17β-dihydroxy-5α-androstano[2,3-*c*]furazan (XI), mp 188—190°/199—200°; testosterone propionate, mp 118.5°—119.5°; methyltestosterone, mp 163—164°.

Male rats of Donryu strain, 23 to 25 days of age and about 50 g in body weight, were used in these experiments, which were obtained from the Central Laboratories for Experimental Animals (Tokyo). The myotrophic and androgenic activities were determined according to the method described in the previous paper.[3]

Results and Discussion

The experimental results are summarized in Table I and II. Compound I showed a favorable separation of myotrophic and androgenic activity when administered subcutaneously, that is, it was equally as myotrophic and 0.1 times as androgenic as testosterone propionate. These properties were similar to those of furazabol reported previously.[3] When given orally, however, myotrophic and androgenic activities of I were below 0.1 times methyltestosterone

Table I. Myotrophic and Androgenic Activities of Various Derivatives of 17β-Hydroxy-5α-androstano[2,3-*c*]furazan (Subcutaneous Injection)

Compound	Total dose (mg/kg)	Organ weight (mg)[a]			Relative potency		M/A ratio
		Levator ani muscle	Ventral prostate	Seminal vesicles	Myotrophic (M)	Androgenic[b] (A)	
Control		17.8±1.5	8.6±0.8	7.9±0.4			
Testosterone propionate	1.5	30.8±2.8	46.0±2.9	39.8±3.0			
	6	40.4±1.6	68.0±6.4	86.8±3.2	1.0	1.0	1.0
	24	53.8±3.9	93.0±6.8	133.5±4.2			
I	1.5	24.0±1.8	12.4±1.0	10.8±0.6			
	6	45.6±2.5	30.6±3.9	29.0±1.9[c]	1.0[d]	0.1[e]	10
	24	53.4±2.0	58.4±3.1	47.0±7.6[f]			
Control		16.8±1.4	9.2±1.0	10.0±0.8			
Testosterone propionate	3	34.6±1.4	46.2±1.6	51.6±1.1			
	9	50.8±1.8	78.2±4.8	106.2±4.7	1.0	1.0	1.0
	27	68.8±4.2	109.4±8.4	165.6±6.8			
II	9	17.2±2.1[N.S.]	11.6±1.2[N.S.]	9.8±0.5[N.S.]			
	27	31.2±1.9[g]	21.2±2.1[h]	15.2±0.5[h]	0.1	<0.1	
III	30	19.5±1.3[N.S.]	7.5±0.5[N.S.]	10.3±0.8[N.S.]	<0.1	<0.1	
IV	30	22.0±0.7[h]	8.5±1.0[N.S.]	9.0±0.4[N.S.]	<0.1	<0.1	
VIII	90	32.4±1.3[g]	21.8±1.5[h]	23.1±1.9[h]	0.03	<0.03	
IX	90	16.3±1.0[N.S.]	9.4±0.8[N.S.]	8.7±0.5[N.S.]	<0.03	<0.03	
X	30	17.0±1.0[N.S.]	11.4±0.7[N.S.]	9.4±0.6[N.S.]	<0.03	<0.03	
	90	27.4±2.0[h]	15.6±1.8[h]	11.2±0.9[N.S.]			
XI	90	21.6±1.0[h]	12.8±1.6[N.S.]	10.8±0.7[N.S.]	<0.03	<0.03	

Five rats were used in each group.

a) mean ± standard error

b) The androgenic potency was expressed as the geometrical mean of the relative potency estimated from the ventral prostate weight and that from the seminal vesicles weight.

c) significant difference ($P<0.05$) to a 1.5 mg/kg group of testosterone propionate (*t*-test)

d) This value was estimated by parallel line assay graphically, and the myotrophic potencies of the other compounds were estimated by *t*-test, since the latter were difficult to be estimated by parallel line assay.

e) The relative potency from the ventral prostate was estimated by parallel line assay graphically, and the potency from the seminal vesicles by *t*-test. The androgenic potencies of the other compounds were estimated by *t*-test, since these potencies were difficult to be estimated by parallel line assay.

f) significant difference ($P<0.05$) to a 6 mg/kg group of testosterone propionate, but non-significant difference ($P>0.05$) to a 1.5 mg/kg group of testosterone propionate (*t*-test)

g) significant difference ($P<0.05$) to a 9 mg/kg group of testosterone propionate, but non-significant difference ($P>0.05$) to a 3 mg/kg group of testosterone propionate (*t*-test)

h) significant difference ($P<0.05$) to a 3 mg/kg group of testosterone propionate (*t*-test)

N.S.: non-significant difference ($P>0.05$) to control (*t*-test)

Table II. Myotrophic and Androgenic Activities of Various Derivatives of 17β-Hydroxy-5α-androstano[2,3-c]furazan (Oral Administration)

Compound	Total dose (mg/kg)	Organ weight (mg)[a]			Relative potency		M/A ratio
		Levator ani muscle	Ventral prostate	Seminal vesicles	Myotrophic (M)	Androgenic[b] (A)	
Control		16.8±1.3	8.8±0.8	8.0±0.3			
Methyltestosterone	90	32.3±1.3	38.3±2.9	30.8±1.8			
	270	40.6±2.9	63.4±3.7	62.2±4.4	1.0	1.0	1.0
	810	53.5±3.5	72.8±7.9	83.8±7.1			
I	810	15.0±1.4[N.S.]	8.0±1.0[N.S.]	9.1±0.5[N.S.]	<0.1	<0.1	
II	810	16.1±1.0[N.S.]	9.2±0.7[N.S.]	9.0±0.5[N.S.]	<0.1	<0.1	
V	810	33.0±2.0[c]	20.4±1.8[d]	15.4±0.7[d]	0.1—0.3	<0.1	
VI	810	27.0±2.0[d]	23.8±1.7[d]	17.5±0.7[d]	<0.1	<0.1	
VII	90	30.8±1.6	20.5±0.3	16.5±1.0			
	270	35.2±2.7	23.2±0.7	20.4±0.8	0.5[e]	0.1	5.0
	810	43.5±1.0	31.3±1.4[f]	32.0±3.5[f]			
Control		15.4±0.4	8.6±0.9	7.9±0.2			
Methyltestosterone	33	21.0±1.0	24.2±3.2	13.0±0.6			
	100	26.0±3.0	25.4±1.1	16.0±0.7	1.0	1.0	1.0
	300	32.2±1.8	41.2±3.4	27.6±2.7			
III	50	24.2±1.8	11.6±0.9	9.4±0.9			
	150	28.2±1.7	20.3±0.4	13.8±0.6	1.0[e]	0.2[e]	5.0
	450	33.4±1.6	26.8±2.1	18.8±1.6			
IV	33	23.8±1.9	18.0±0.7	12.4±0.7			
	100	35.4±2.0	23.2±2.2	16.2±0.8	3.3[e]	0.8[e]	4.1
	300	42.6±1.9	35.0±0.7	31.2±1.2			

Five rats were used in each group.

a) mean ± standard error

b) The androgenic potency was estimated by the same method as described in Table I.

c) significant difference ($P<0.05$) to a 810 mg/kg group of methyltestosterone, but non-significant difference ($P>0.05$) to 90 and 270 mg/kg groups of methyltestosterone (t-test)

d) significant difference ($P<0.05$) to a 90 mg/kg group of methyltestosterone (t-test)

e) These values were estimated by parallel line assay graphically, and myotrophic and androgenic potencies of the other compounds by t-test, since the latter were difficult to be estimated by parallel line assay.

f) significant difference ($P<0.05$) to a 270 mg/kg group of methyltestosterone, but non-significant difference ($P>0.05$) to a 90 mg/kg group of methyltestosterone (t-test)

N.S.: non-significant difference ($P>0.05$) to control (t-test)

although furazabol[3] was 2.7 to 3.3 times as myotrophic and 0.73 to 0.94 times as androgenic as methyltestosterone. These results indicate that I has much less activities than furazabol when compared orally. Manson, *et al.*[8] have reported that 17β-hydroxy-5α-androstano [2,3-d]isoxazole was comparable in myotrophic and androgenic activities to the corresponding 17α-methyl analogue when administered parenterally, but inactive when given orally. Here, since II was almost inactive, the decrease in the activities of I by oral route is probably due to its transformation to II in the liver, about which the following paper will show the experimental evidence.

On the other hand, III and IV were markedly effective when given orally although their subcutaneous activities were very low. It should be noted that these compounds, in oral experiments, were not only highly effective in myotrophic action but also had a relatively low androgenic action. Several authors[9,10] have already reported that oral activities of 17β-

8) A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackerman, D.F. Page, J.W. Dean, D.K. Phillips, G.O. Potts, A. Arnold, A.L. Beyler, and R.O. Clinton, *J. Med. Chem.*, **6**, 1 (1963).

9) A. Ercoli, R. Gardi, and R. Vitali, *Chem. Ind.* (London), **1962**, 1284.

10) A.D. Cross, I.T. Harrison, P. Crabbé, F.A. Kincl, and R.I. Dorfman, *Steroids*, **4**, 229 (1964).

hydroxy–3–oxo–steroids were remarkably enhanced by etherification of the 17β–hydroxy group. For example, 2′–tetrahydropyranyl ether[10] of 2α–methyl–5α–dihydrotestosterone has been shown to possess a markedly enhanced activity relative to the corresponding hydroxy compound when given orally although it had a low activity subcutaneously.

In addition, some 17α–substituted derivatives of I were also examined. As shown in Table II, compounds V,VI, and VII were found to have a much less activity than methyltestosterone when compared orally. It is interesting that these compounds are less active than methyltestosterone while 17α–methyl derivative (furazabol) is more active than methyltestosterone in myotrophic effect orally. It has been known that the myotrophic and androgenic activities of 17α–ethyltestosterone are lower than those of methyltestosterone and that, in 19–nortestosterone, when the 17α–alkyl side chain is lengthened to the propyl and beyond, the activities decrease although 17α–methyl and 17α–ethyl analogues have the same order of the activities.[11,12] Furthermore, an example of the decrease of the activities by introduction of unsaturated chain, such as a vinyl and an ethynyl group, into 17α–position has been shown also in 19–nortestosterone.[11,12] Some of 16–methylene compounds have been reported to have a high anabolic activity.[13] However, 16–methylene (VIII), 16β–methyl (IX), 16α–(X), and 16β–hydroxy (XI) derivatives of I were much less active than I by subcutaneous administration.

Acknowledgement The authors are very grateful to Dr. T. Ishiguro, President of this Company, for his unfailing encouragements.

11) V.A. Drill and B. Riegel, "Recent Progress in Hormone Research," ed. by G. Pincus, XIV, Academic Press Inc., New York, 1958, p. 29.
12) F.J. Saunders and V.A. Drill, *Endocrinol.*, **58**, 567 (1956).
13) U.S. Patent 3117060 [*C.A.*, **61**, 12060 (1964)].