

Synthesis and Structure-Activity Relationships of 7 α -Alkylthioandrostanes

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In order to examine the relationships between the structure and activity in anabolic steroids, 17 α -methyltestosterone and 17 α -methyl dihydrotestosterone derivatives containing 7 α -alkylthio and/or 7 α -arylthio groups were synthesized. Some of these compounds possess high myotrophic activity with a favorable myotrophic-androgenic ratio. Preparation of androstano-isoxazoles and isoxazolines having the 7 α -ethylthio group was also described.

Ringold's hypothesis²⁾ from biological activity of modified androgens that specific α -face adsorption of the androgen molecule on a cellular or enzyme surface is required to elicit a basal androgen response seems to be inconsistent with the hormonal activity of 7 α -methyl testosterone³⁾ sterically hindered on a receptor site, but little is known of the effects of modification of 7-*axial* moiety on biological activities. Introduction of an alkylthio group of different size into the 7 α position of the steroid molecule might lead to useful products for the elucidation of the mechanism of biological action. The purpose of the present work was to prepare several types of saturated and unsaturated 7 α -alkylthioandrostanes for examination of the relationships of myotrophic and androgenic activities with their structures.

Preparation of 7 α -Alkylthioandrostane Derivatives

A series of 7 α -alkylthio-17 β -hydroxy-17 α -methylandro-4-en-3-ones (IIa—IIm) were synthesized from 17 β -hydroxy-17 α -methylandro-4,6-dien-3-one (I) with various mercaptans in the presence of catalytic strongly basic anion-exchange resin or sodium methylate in fairly good yields. Reduction of 7 α -alkylthioandro-4-en-3-ones (IIa—IIg) with lithium in liquid ammonia proceeded smoothly to give the corresponding 5 α -androstanes (IIIa—IIIg) without S-alkyl cleavage. Under similar condition, 7 α -allylthio (IIj) and 7 α -benzylthio androstane (IIm) yielded 7 α -mercapto derivative (IIIa) accompanied with a reductive cleavage of allylic and benzylic positions, whereas the 7 α -phenylthio derivative (III) formed 17 β -hydroxy-17 α -methylandrostan-3-one under cleavage at the C₇-S chain. Condensation of 7 α -alkylthio-5 α -androstan-3-ones (IIIa—IIIg) with ethyl formate in the presence of sodium hydride afforded 2-hydroxymethylene-3-ketosteroids (IVa—IVg), which were easily converted to [3,2-*c*]pyrazoles (Va—Vg) by treatment with hydrazine according to Clinton's method.⁴⁾ The physical constants and the spectroscopic data of these compounds are listed in Table I.

A series of 7 α -ethylthiosulfinyl (VIa, VIIa and IXa) and 7 α -ethylsulfonyl analogs (VIb, VIIb and IXb) were obtained by oxidation of the corresponding 7 α -ethylthio derivatives (IIc, IIIc and Vc) with monoperoxyphthalic acid (MPA) in a similar method reported by Schaub,

1) Location: *Kami-Ebie 2, Fukushima-Ku, Osaka.*

2) H.J. Ringold, "Mechanism of Action of Steroid Hormones," ed. by C.A. Villee and L.L. Engel, Pergamon Press, New York, N.Y., 1961, p. 200.

3) J.A. Campbell and J.C. Babcock, *Hormonal Steroids*, 2, 59 (1965).

4) R.O. Clinton, A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackerman, D.F. Page, J.W. Dean, W.B. Dickinson, and C. Carabateas, *J. Am. Chem. Soc.*, 83, 1478 (1961).

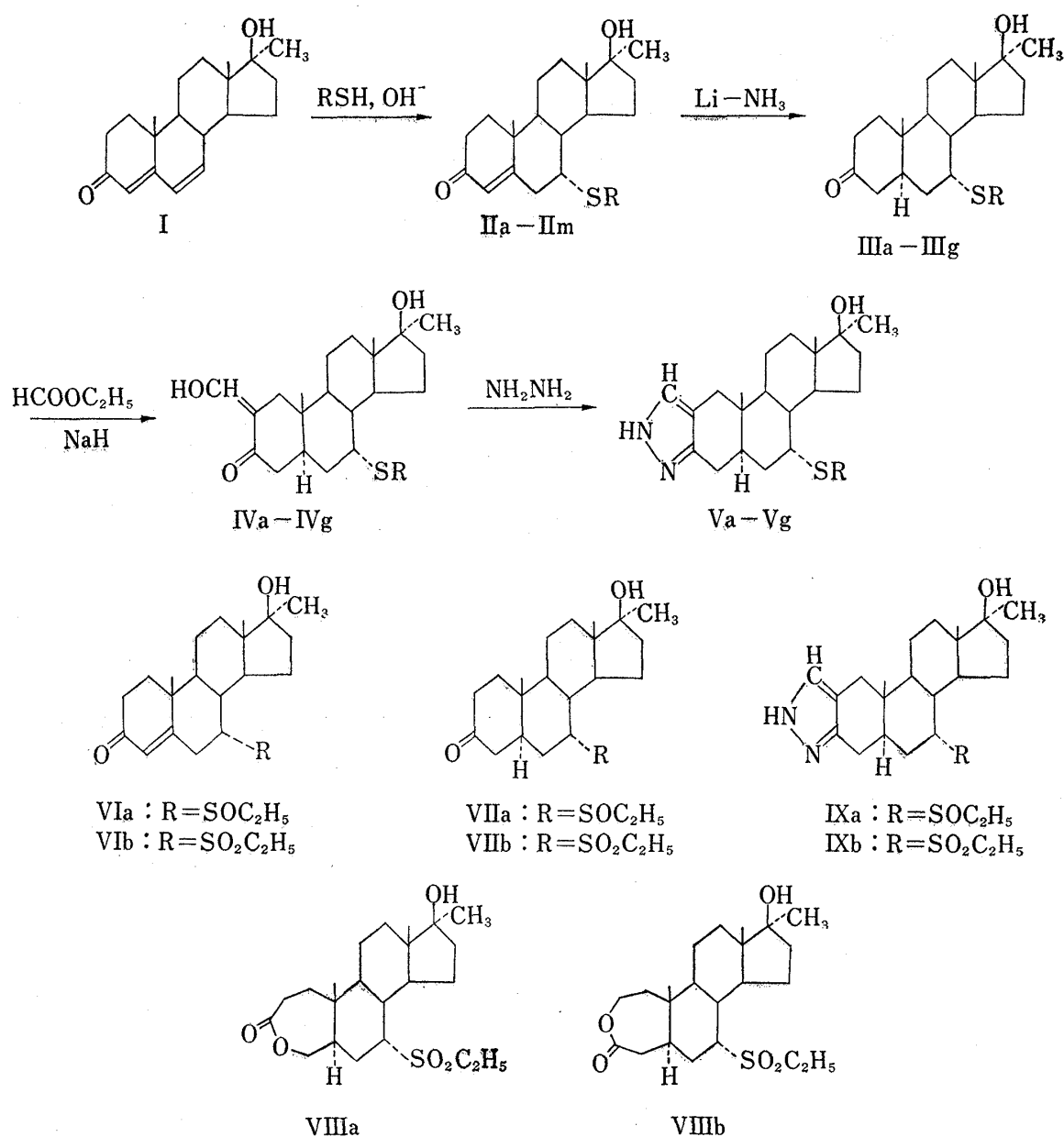


Chart 1

*et al.*⁵⁾ Treatment of IIIc with excess of MPA afforded a mixture of A-homo-oxasteroids (VIIIa and VIIIb), whose structures were confirmed by comparison of their nuclear magnetic resonance (NMR) spectra with those of A-homo-oxasteroids in the cholestane series reported by Hara, *et al.*⁶⁾

Preparation of 7a-Ethylthiosteroidal Isoxazoles

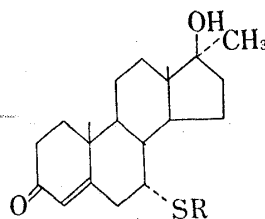
It has been reported⁷⁾ that a number of androstanes having an isoxazole ring at the 2,3 positions can be obtained from the reaction of 2-hydroxymethylene-3-oxosteroid with hydroxylamine and the formation ratio between the products in this reaction is dependent upon

5) R. E. Schaub and M. J. Weiss, *J. Org. Chem.*, **27**, 2221 (1962).

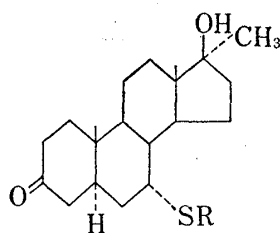
6) S. Hara and N. Matsumoto, *Yakugaku Zasshi*, **85**, 48 (1965).

7) a) A.J. Manson, F.W. Stonner, H.C. Neumann, R.G. Christiansen, R.L. Clarke, J.H. Ackermann, 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); b) J.A. Zderic, O. Halpern, H. Carpio, A. Ruiz, D.C. Limon, L. Magaña, H. Jiménez, A. Bowers, and H.J. Ringold, *Chem. Ind. (London)*, **1960** 1625; c) E. Marchetti and P. Donini, *Gazz. Chim. Ital.*, **86**, 1133 (1961).

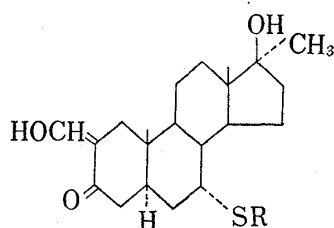
TABLE I.



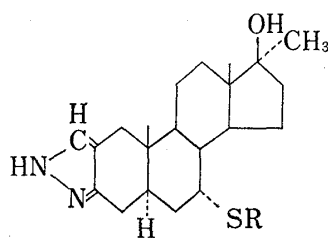
Com- pound No.	R	mp (°C)	Formula	Analysis (%)						[α] _D ^{CHCl₃}	λ _{max} ^{EtOH} mμ (ε)
				Calcd.			Found				
				C	H	S	C	H	S		
IIa	H ^{a)}	165—168	C ₂₀ H ₃₀ O ₂ S	71.81	9.04	9.59	71.93	9.05	9.50	+48.5 (c=1.32)	239 (13400)
IIb	CH ₃ ^{a)}	195—200	C ₂₁ H ₃₂ O ₂ S	72.36	9.26	9.20	72.17	9.05	9.32	-10.5 (c=1.60)	242 (16500)
IIc	C ₂ H ₅ ^{a)}	182—185	C ₂₂ H ₃₄ O ₂ S	72.88	9.45	8.84	73.17	9.74	8.43	+14.4 (c=1.32)	242 (15500)
IId	n-C ₃ H ₇	129—131	C ₂₃ H ₃₆ O ₂ S	73.35	9.64	8.51	73.30	9.76	8.37	-41.0 (c=1.80)	242 (15500)
IIe	iso-C ₃ H ₇	183—187	C ₂₃ H ₃₆ O ₂ S	73.35	9.64	8.51	73.63	9.58	8.58	-39.0 (c=1.18)	242 (16900)
IIf	n-C ₄ H ₉	107—109	C ₂₄ H ₃₈ O ₂ S	73.79	9.81	8.21	74.05	9.79	8.29	-41.5 (c=1.11)	242 (13600)
IIg	tert-C ₄ H ₉	224—228	C ₂₄ H ₃₈ O ₂ S	73.79	9.81	8.21	73.83	9.92	7.93	-34.7 (c=0.93)	243 (15700)
IIh	COCH ₃ ^{a)}	175—177	C ₂₂ H ₃₂ O ₃ S	70.17	8.57	8.52	70.12	8.47	8.42	-81.8 (c=0.99)	239 (19300)
IIi	CH ₂ CH ₂ SH	142—144	C ₂₂ H ₃₄ O ₂ S	66.96	8.68	16.25	66.89	8.67	15.72	-63.0 (c=1.19)	241 (15800)
IIj	CH ₂ CH=CH ₂	132—134	C ₂₃ H ₃₄ O ₂ S	73.75	9.15	8.56	73.85	9.13	8.71	-42.0 (c=1.12)	242 (15400)
IIk	CH ₂ COOC ₂ H ₅	172—175	C ₂₄ H ₃₆ O ₄ S	68.53	8.63	7.62	68.76	8.59	7.49	-66.2 (c=1.06)	241 (16600)
IIl	C ₆ H ₅	235—245 (decomp.)	C ₂₆ H ₃₄ O ₂ S	76.05	8.35	7.81	76.25	8.54	7.71	-104.0 (c=1.08)	246 (16500)
IIm	CH ₂ C ₆ H ₅	174—178	C ₂₇ H ₃₆ O ₂ S	76.45	8.55	7.55	76.44	8.74	7.40	-105.0 (c=1.52)	243 (17800)



IIIa	H	168—171	C ₂₀ H ₃₂ O ₂ S	71.38	9.04	9.59	71.58	9.58	9.27	-38.0 (c=1.06)	
IIIb	CH ₃	201—203	C ₂₁ H ₃₄ O ₂ S	71.95	9.78	9.15	72.21	9.74	9.20	-77.0 (c=1.58)	
IIIc	C ₂ H ₅	149—152	C ₂₂ H ₃₆ O ₂ S	72.47	9.95	8.80	72.60	9.87	8.69	-93.9 (c=1.33)	
IIId	n-C ₃ H ₇	120—130	C ₂₃ H ₃₈ O ₂ S	72.96	10.12	8.47	72.75	10.10	8.44	-79.5 (c=1.91)	
IIIe	iso-C ₃ H ₇	185—188	C ₂₃ H ₃₈ O ₂ S	72.96	10.12	8.47	73.22	10.36	8.65	-38.3 (c=1.95)	
IIIf	n-C ₄ H ₉	114—117	C ₂₄ H ₄₀ O ₂ S	73.41	10.27	8.17	73.22	10.23	7.71	-82.6 (c=1.18)	
IIIg	tert-C ₄ H ₉	206—208	C ₂₄ H ₄₀ O ₂ S	73.41	10.27	8.17	73.41	10.49	7.77	-79.4 (c=1.38)	



IVa	H	140—143	$C_{21}H_{32}O_3S \cdot \frac{1}{3}\text{acetone}$	68.83	8.93	8.35	68.61	9.10	8.40	-25.6 ($c=1.33$)	285 (8900)
IVb	CH_3	189—192	$C_{22}H_{34}O_3S$	69.80	9.05	8.47	69.62	9.25	8.38	-53.2 ($c=1.30$)	283 (9300)
IVc	C_2H_5	168—171	$C_{23}H_{36}O_3S$	70.36	9.24	8.17	70.28	9.19	8.10	-64.5 ($c=0.93$)	278 (12100)
IVd	$n\text{-}C_3H_7$	197—200	$C_{24}H_{38}O_3S$	70.89	9.42	7.89	70.90	9.42	7.64	-70.5 ($c=1.17$)	285 (9700)
IVe	$iso\text{-}C_3H_7$	186—188	$C_{24}H_{38}O_3S$	70.89	9.42	7.89	70.56	9.46	7.69	-69.0 ($c=1.52$)	280 (11500)
IVf	$n\text{-}C_4H_9$	187—190	$C_{25}H_{40}O_3S$	71.38	9.59	7.62	71.60	9.45	7.47	-64.9 ($c=1.40$)	281 (10200)
IVg	$tert\text{-}C_4H_9$	181—185	$C_{25}H_{40}O_3S$	71.38	9.59	7.62	71.18	9.51	7.36	-62.5 ($c=0.79$)	285 (8900)



Compound No.	R	mp (°C)	Formula	Analysis (%)								$[\alpha]_D^{CHCl_3}$	λ_{max}^{EtOH} (mμ)
				Calcd.				Found					
				C	H	N	S	C	H	N	S		
Va	H	247—249 (decomp.)	C ₂₁ H ₃₂ N ₂ OS	69.95	8.95	7.77	8.89	69.82	9.04	7.96	8.62	-14.2 (c=1.06)	224 (5200)
Vb	CH ₃	155—158	C ₂₂ H ₃₄ N ₂ OS	70.54	9.15	7.48	8.56	70.23	9.35	7.22	8.20	-39.0 (c=1.31)	224 (4700)
Vc	C ₂ H ₅	149—151	C ₂₃ H ₃₆ N ₂ OS	71.08	9.34	7.21	8.25	71.02	9.43	7.02	8.43	-60.4 (c=1.01)	224 (5500)
Vd	n-C ₃ H ₇	135—137	C ₂₄ H ₃₈ N ₂ OS	71.59	9.51	6.96	7.96	71.69	9.59	6.90	7.80	-54.0 (c=1.85)	225 (5000)
Ve	iso-C ₃ H ₇	152—155	C ₂₄ H ₃₈ N ₂ OS	71.59	9.51	6.96	7.96	71.49	9.55	6.75	7.60	-54.2 (c=1.46)	225 (4900)
Vf	n-C ₄ H ₉	130—134	C ₂₅ H ₄₀ N ₂ OS	72.06	9.68	6.72	7.70	71.90	9.89	6.62	7.67	-53.8 (c=1.02)	225 (4800)
Vg	tert-C ₄ H ₉	242—252 (decomp.)	C ₂₅ H ₄₀ N ₂ OS· 1/2H ₂ O	70.54	9.71	6.58	7.53	70.32	9.58	6.29	7.32	-49.7 (c=0.70)	223 (4900)

a) IIa: mp 158—160°, λ_{max}^{EtOH} mμ (ε): 237, 238 (14450); IIb: mp 196—197°, $[\alpha]_D$ -32° (dioxane), λ_{max}^{EtOH} mμ (ε): 240 (16000); IIc: mp 180—182°, $[\alpha]_D$ -55° (dioxane), λ_{max}^{EtOH} mμ (ε): 241 (15600); IIh: mp 173—174°, $[\alpha]_D$ -75° (dioxane), λ_{max}^{EtOH} mμ (ε): 238.5 (9300) (J.M. Krämer, K. Brückner, K. Irmscher, and K.-H. Brok, *Chem. Ber.*, **96**, 2803 (1963))

pH, solvent and temperature. We wish now further to report an additional study of steroidal isoxazoles and the related compounds having 7 α -ethylthio group.

The reaction of 2-hydroxymethylene-17 β -hydroxy-17 α -methylandrostan-3-one (X) with hydroxylamine hydrochloride in refluxing alcoholic solution containing sodium acetate is known to afford 17 β -hydroxy-17 α -methylandrostan-3-one[3,2-*c*]-5'-hydroxy- Δ^2 -isoxazoline (XI) and 17 β -hydroxy-17 α -methylandrostan-3-one[2,3-*d*]isoxazole (XII), together with a small amount of 17 β -hydroxy-17 α -methylandrostan-3-one[3,2-*c*]isoxazole (XIII).^{7a)} However, when 2-hydroxymethylene-7 α -ethylthio-17 β -hydroxy-17 α -methylandrostan-3-one (IVc) was used under similar condition, two isomeric isoxazolines, 7 α -ethylthio-17 β -hydroxy-17 α -methylandrostan-3-one[3,2-*c*]-5'-hydroxy- Δ^2 -isoxazoline (XIV) and 3 β ,17 β -dihydroxy-7 α -ethylthio-17 α -methylandrostan-3-one[2,3-*d*]-5'-hydroxy- Δ^2 -isoxazoline (XV) were obtained in 20 and 12% yields, respectively. By acid treatment the former compound was readily dehydrated to form [3,2-*c*]isoxazole (XVI), and acetylation of XIV with acetic anhydride in pyridine afforded 5'-acetate (XVII). The infrared (IR) spectrum of XIV showed an absorption band at 1643 cm⁻¹ due to the >C=N- group and there was no selective absorption above 220 m μ in the ultraviolet (UV) spectrum. These data of XIV were quite similar to those of XI described above. However, XIV was most likely shown to be a mixture of structure XIVa and XIVb by means of NMR spectrum as follows.

The stereochemistry of 5'-hydroxy group of XI was shown to be β -configuration from the coupling constant ($J=2$ cps) of 5'-proton in its 5'-acetate and mechanical consideration of elimination of the 5'-hydroxy group by Manson, *et al.*^{7a)} However, an unexpectedly large coupling constant ($J=7.0$ cps) of the 5'-proton was observed in the 5'-acetate of 7 α -ethylthio-17 β -hydroxy-17 α -methylandrostan-3-one[3,2-*c*]isoxazoline (XIV) obtained. This discrepancy of the coupling constant between the two acetates from XI and XIV seems to due to the difference of the configuration at C-5'. Based on the observation⁸⁾ that the coupling constant of C-2 proton coupled with C-3 proton in *cis* 3-methylproline derivatives was greater than that of *trans* isomer, the stereochemistry of the 5'-proton in the acetate of XIV having larger coupling constant and of that in the acetate of XI having a smaller coupling constant were assumed to be *cis* and *trans* relation to the proton at C-2, respectively. Consequently, the 5'-acetate of XIV may be represented by the structure XVIIb.

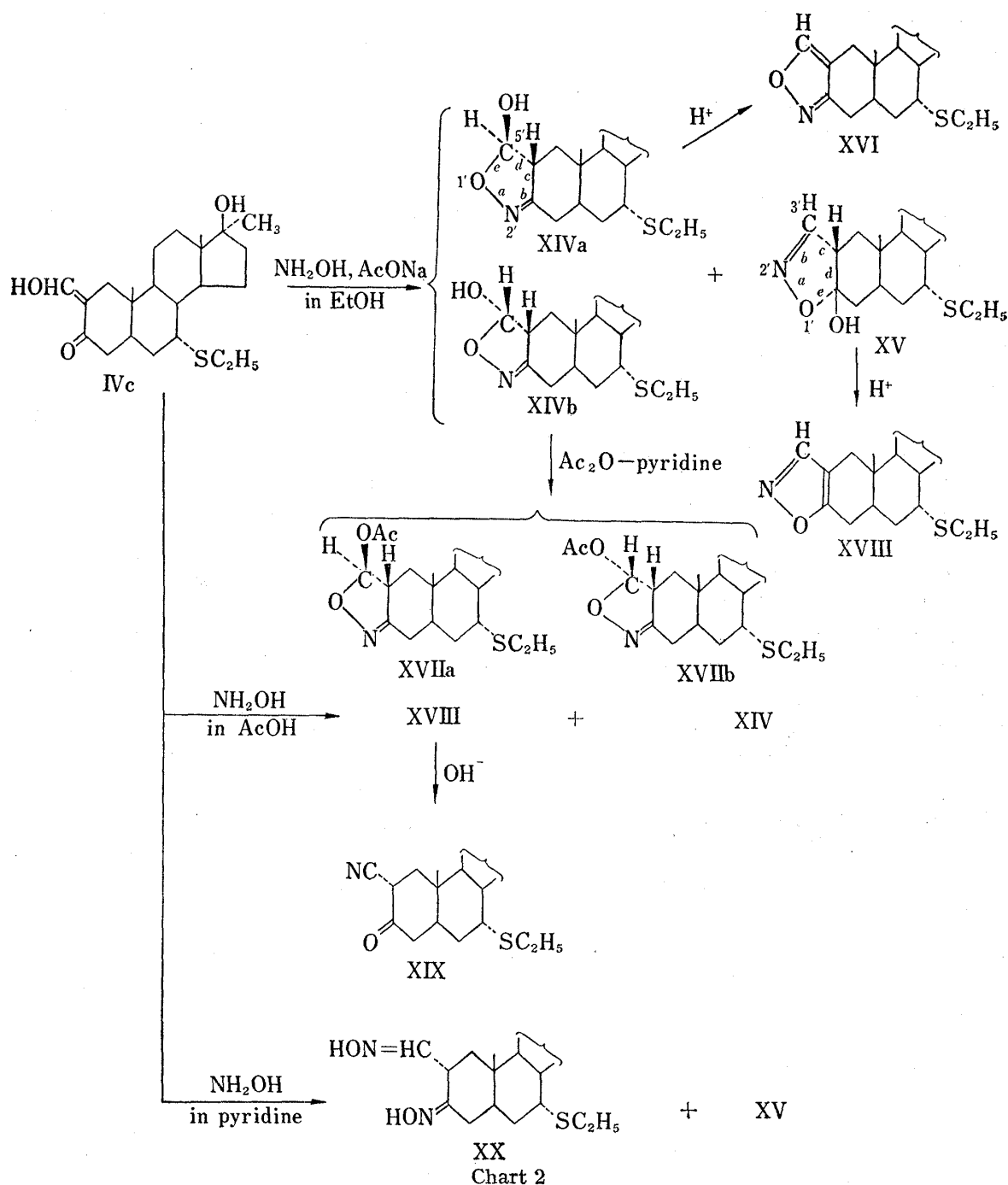
Although an attempt to isolate another isomeric acetate (XVIIa) corresponded to XVIIb was unsuccessful, the acetylation product of XIV which was homogeneous on thin-layer chromatography (TLC) exhibited a doublet ($J=7.0$ cps) at 3.36 τ due to the 5'-proton besides a weak doublet ($J=2.0$ cps) at 3.69 τ , and the signal of the 19-methyl group also showed a doublet splitting pattern at 9.08 and 9.03 τ , in which the latter signal was assignable to the 19-methyl group of XVIIa due to the long range deshielding of the acetoxy group at C-5'. These results indicated that the 5'-acetate of XIV consists of a mixture of 5' α and 5' β -acetoxy derivatives (XVIIa and XVIIb). Since a similar NMR pattern was observed in the case of the 5'-acetate of XI, it was therefore also suggested to be a mixture of 5' α and 5' β -epimers.

In addition, also the [3,2-*c*]-5'-hydroxy- Δ^2 -isoxazoline (XIV), which was confirmed to be homogeneous on TLC, exhibited two doublets at 4.55 ($J=2.0$ cps) and 4.39 τ ($J=7.0$ cps) due to the proton at C-5', and the signal of the 19-methyl group was appeared at 9.12 and 9.07 τ .⁹⁾ The [3,2-*c*]isoxazoline (XIV) may consequently be a mixture of stereochemical isomers at C-5' (XIVa and XIVb) in comparison with the data of its 5'-acetate described above. The isoxazoline (XI) with melting point at 233—237° first reported by Manson, *et al.*^{7a)} is probably a mixture of two isomers at C-5'.

The [2,3-*d*]isoxazoline (XV) obtained above was also readily dehydrated with acid to give 7 α -ethylthio-17 β -hydroxy-17 α -methylandrostan-3-one[2,3-*d*]isoxazole (XVIII). The ultraviolet

8) A.B. Mauger, F. Irreverre, and B. Witkop, *J. Am. Chem. Soc.*, **88**, 2019 (1966).

9) Their NMR spectrum were measured in DMSO-d₆ solution.



spectrum of XV revealed no absorption band above $220\text{ m}\mu$ and its infrared spectrum showed absorption bands at 3300 (OH) and 1623 cm^{-1} ($>\text{C}=\text{N}-$). In the NMR spectrum of XV an olefinic proton at C-3' appeared as a feebly resolved doublet ($J=1.5\text{ cps}$) at 2.48τ , coupled with the proton at C-2. Although a signal of 5'-hydroxy group is indiscernible, the structure postulated for XV is consistent with the above results.

Reaction of 2-hydroxymethylene-7 α -ethylthio-17 α -methyldihydrotestosterone (IVc) with hydroxylamine hydrochloride in acetic acid without sodium acetate at room temperature yielded the 7 α -ethylthio[2,3-*d*]isoxazole (XVIII) and 7 α -ethylthio[3,2-*c*]isoxazoline (XIV) in 80 and 14% yields, respectively. The structure of XVIII was demonstrated by its ready conversion to 2 α -cyano-3-oxosteroid (XIX). Finally, when IVc was treated with excess of hydroxylamine hydrochloride in pyridine, two crystalline products were obtained, in which less soluble substance in benzene was found to contain two nitrogens in the molecule from

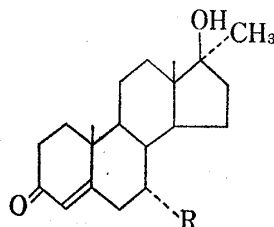
elementary analysis. Its infrared spectrum did not exhibit ketone absorption but the $>\text{C}=\text{N}$ -group at 1656 cm^{-1} . The NMR spectrum showed a doublet ($J=7.0\text{ cps}$) at 3.26τ and two singlets at -0.51 and -0.64τ attributable to an azomethine proton at C-2 and hydroxy protons of oxime, respectively. Accordingly, the structure of the dioxime was assigned as XX presented in Chart 2. Another one isolated from benzene fraction was identical with the [2,3-*d*]isoxazoline (XV) by comparison with TLC and infrared spectrum.

Anabolic and Androgenic Activities of 7 α -Alkylthioandrostane Derivatives

The experiments were performed according to the method reported by Hershberger, *et al.*¹⁰⁾ on immature castrated male rat weighing about 50 g. Five animals for each sample were employed. The steroids, dissolved in SV solution,¹¹⁾ were administered subcutaneously at $1.5\text{ }\mu\text{moles}$ per rat once daily for 7 days, beginning after the castration. Testosterone propionate (TP) as the standard was administered subcutaneously in equimolecular dose. The increase in the weight of the levator ani muscle compared with that of the control animal was used as the indication of myotrophic activity. The weight increase of the ventral prostate and seminal vesicles was used to calculate the androgenic activity. The relative myotrophic and androgenic potencies were given in terms of per cent of the activity of TP. Index value (myotrophic/androgenic ratio) means the relative myotrophic response per geometrical mean value of the ventral prostate and seminal vesicles responses.

In the series of Δ^4 -androstenes 7 α -alkylthio group did not enhance any of their anabolic and androgenic activities as shown in Table II. Although the 7 α -ethylthio derivative (IIc) exhibited a high myotrophic/androgenic ratio ($\text{M/A}=8.3$), its myotrophic activity was only

TABLE II. Myotrophic and Androgenic Activities of 7 α -Alkylthio- Δ^4 -androsten-3-ones^{a)}



Compound	Myotrophic activity levator ani	Androgenic activity		Index (myotrophic/ androgenic)
		Ventral prostate	Seminal vesicles	
Testosterone propionate	100	100	100	1
R=SH ^{b)} (IIa)	23.7	4.9	nil	
SMe ^{b)} (IIb)	93.2	61.9	32.1	2.0
SEt ^{b)} (IIc)	72.6	9.7	7.7	8.3
S- <i>n</i> -Pr (IId)	40.6	16.4	4.6	3.9
S-iso-Pr (IIe)	24.7	9.2	1.4	4.7
S- <i>n</i> -Bu (IIf)	64.5	25.5	6.1	4.0
S- <i>tert</i> -Bu (IIg)	nil	nil	nil	
SPh (IIh)	nil	nil	nil	
SBz (IIi)	nil	nil	nil	
CH ₃ ^{c)} (bolasterone)	112.2	120.2	153.6	0.82

a) The steroids were administered subcutaneously at $1.5\text{ }\mu\text{moles}$ per rat daily for 7 days.

b) H. Kraft and K. Brückner, *Arzneimitt. Forsch.*, **14**, 328 (1964)

c) J.C. Stucki, G.W. Duncan, and S.C. Lyster, *Hormonal Steroids*, **2**, 119 (1965)

10) L.G. Hershberger, E.G. Shipley, and R.K. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

11) The steroids were dissolved or suspended in SV-No. 17874 (Dorfman, 1962) consisting of an aqueous solution of sodium chloride (0.9%), polysorbate 80 (0.4%), carboxymethylcellulose (0.5%), and benzyl alcohol (0.9%).

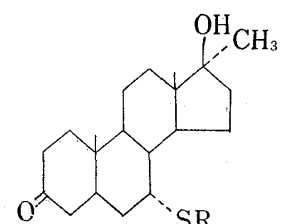
72.6% of that of TP. The increase in the length of 7 α -thioalkyl carbon chain seems to result in the decrease of the biological activity. While the increase in the androgenic activity occurred in general on reduction of the double bond between C-4 and C-5 in testosterone derivatives to the corresponding androstan-3-ones, there was also the same case in the 7 α -alkylthioandrostan-3-one derivatives compared with the corresponding androstene series as shown in Table III. Among these derivatives the 7 α -isopropylthio derivative (IIIe) displayed a favourable anabolic potency as compared with that of 7 α ,17 α -dimethyltestosterone (bolasterone) presented in Table II. From these data, the bulkiness of 7 α -substituent in the 17 α -methyltestosterone and 17 α -methyl-dihydrotestosterone was found not to be a main factor on the biological activities.

It has been reported¹²⁾ that the introduction of a pyrazole ring into C-2,3 positions of 17 α -methyl-dihydrotestosterone afforded the potent anabolic compound (*e.g.* 17 β -hydroxy-17 α -methyl-5 α -androstan-3-one[3,2-*c*]pyrazole (stanozolol)). The additional incorporation of lower alkylthio group at C-7 of stanozolol resulted in a better separation of the myotrophic and androgenic activity with a high myotrophic potency than the parent steroid as shown in Table IV.

The most interesting member of the [3,2-*c*]pyrazole series in terms of the separation of the anabolic and androgenic activities was 7 α -ethylthio-17 β -hydroxy-17 α -methyl-androstan-3-one[3,2-*c*]pyrazole (Vc). It was an approximately 1.43 times as myotrophic and 0.26 times as androgenic as methyltestosterone, whereas stanozolol was 1.1 times as myotrophic and 0.44 times as androgenic as methyltestosterone on oral administration. In the pyrazole series, when the size of 7 α -alkylthio group was larger than that of ethylthio group, remarkable reduction was observed in the biological activities.

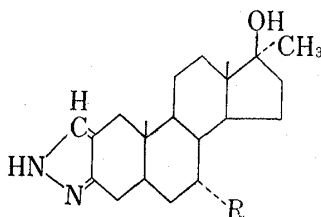
In the 2-hydroxymethylene-3-oxosteroids, the introduction of the alkylthio group into C-7 position did not enhance their biological activities. Finally, also oxidation of ethylthio group to sulfinyl and sulfonyl group did not elicit any significant activity on the parent compounds as shown in Table V.

TABLE III. Myotrophic and Androgenic Activities of 7 α -Alkylthio-5 α -androstan-3-ones^{a)}



Compound	Myotrophic activity levator ani	Androgenic activity		Index (myotrophic/ androgenic)
		Ventral prostate	Seminal vesicles	
Testosterone propionate	100	100	100	1
R=H (IIIa)	48.8	134.5	46.2	0.5
Me (IIIb)	33.1	48.4	19.9	1.0
Et (IIIc)	2.3	34.6	4.6	0.1
<i>n</i> -Pr (IIId)	17.8	9.2	4.3	2.6
iso-Pr (IIIe)	102.2	46.0	14.4	3.4
<i>n</i> -Bu (IIIf)	slight	slight	slight	
<i>tert</i> -Bu (IIIg)	slight	slight	slight	

a) The compounds were administered subcutaneously.

TABLE IV. Myotrophic and Androgenic Activities of 7 α -Alkylthio-5 α -androstando[3,2-*c*]pyrazoles^{a)}

Compound	Myotrophic activity levator ani		Androgenic activity				Index (myotrophic/ androgenic)	
			Ventral prostate		Seminal vesicles			
	SC	PO	SC	PO	SC	PO	SC	PO
Testosterone propionate	100		100		100		1	
Methyltestosterone		100		100		100		1
R=SH (Va)	102.5	384	75.1	131	36.0	210	1.85	2.2
SMe (Vb)	31.0	106.7	11.1	17.2	3.0	56.4	4.3	2.9
SEt (Vc)	54.7	143.3	16.4	11.9	6.3	39.8	4.8	5.6
S- <i>n</i> -Pr (Vd)	nil		nil		nil			
S-iso-Pr (Ve)	slight		nil		nil			
S- <i>n</i> -Bu (Vf)	nil		weak		weak			
S- <i>tert</i> -Bu (Vg)	35.3		8.9		7.3		4.3	
H (stanozolol)	77.8	109.5	30.9	15.4	29.1	62.6	2.6	2.8

a) The steroids were administered subcutaneously (SC) at 1.5 μ moles per rat daily for 7 days and orally (PO) at 1.0 mg per rat daily for 7 days.

TABLE V. Myotrophic and Androgenic Activities of Miscellaneous Steroids^{a)}

Compound	Myotrophic activity levator ani	Androgenic activity		Index (myotrophic/ androgenic)
		Ventral prostate	Seminal vesicles	
X ^{b)} (Oxymetholone)	73.8	37.8	11.9	3.0
IVb	30.7	21.5	2.2	2.6
IVc	13.0	4.9	0.7	4.6
XII	77.4	68.2	68.5	1.1
XVIII	43.2	18.5	19.1	2.3
XVI	11.8	4.5	5.5	2.4
XIV	51.5	22.5	17.7	2.5
XV	13.2	2.9	28.2	0.9
Ka	26.3	14.4	4.7	2.7
Kb	nil	nil	slight	
XIX	nil	nil	nil	
Testosterone propionate	100	100	100	1

a) The Steroids were administered subcutaneously at 1.5 μ moles per rat daily for 7 days.

b) R.I. Dorfman and F.A. Kincl, *Endocrinology*, **72**, 259 (1963).

Experimental¹³⁾

General Procedure for the Preparation of 7 α -Alkylthioandrostande Derivatives. Preparation of 7 α -Alkylthio and 7 α -Arylthio- Δ^4 -androstene-3-ones (IIa—IIm)—Method A: To a solution of 0.03 moles of 17 β -hydroxy-17 α -

- 13) Melting points are uncorrected. IR spectra were determined in KBr disk and UV spectra in EtOH solution. Optical rotations were measured in CHCl₃ solution at 20° and NMR spectra were recorded on a Varian A-60 spectrometer in CDCl₃ containing tetramethylsilane as internal standard unless otherwise indicated.

methylandrosta-4,6-dien-3-one (I) in 200 ml of corresponding mercaptan was added 5 g of anion exchange resin (hydroxide form of Amberlite IRA-411). The suspension was stirred at room temperature for 24 hr or heated under reflux for 5 hr. The reaction mixture was then filtered and the filtrate was evaporated *in vacuo*. The resulting crude product was recrystallized from acetone or acetone-hexane to give the corresponding 7 α -alkylthio and/or 7 α -arylthio steroid. Yield, 80–90%.

Method B: To a solution of 0.03 moles of I in a mixture of mercaptan (20 ml) and dioxane (100 ml) was added 3 g of MeONa. The mixture was stirred at room temperature for 10 hr, diluted with water and extracted with ether. After working up as usual, the resulting crude product was recrystallized from the solvent as described in Method A. The corresponding 7 α -alkylthio and/or 7 α -arylthio steroid was obtained in 80–90% yield.

Preparation of 7 α -Alkylthio-5 α -androstan-3-ones (IIIa–IIIg)—Reduction of 7 α -alkylthio- and/or 7 α -arylthio- Δ^4 -3-oxosteroids with lithium in liquid ammonia was carried out in the similar way reported by Weisenborn, *et al.*¹⁴⁾ The resulting crude product except 7 α -mercapto derivative (IIIa) was purified with sodium metabisulfite and formalin,¹⁵⁾ followed by recrystallization from AcOEt or acetone-hexane to give the corresponding 7 α -alkylthio-5 α -androstan-3-one. Yield, 60–70%.

On the other hand, reaction product obtained from the 7 α -mercapto, 7 α -allylthio and 7 α -benzylthio- Δ^4 -3-oxosteroids was purified by chromatography on silica gel. Elution with 5% ether-benzene afforded the 7 α -mercapto steroid (IIIa), which was recrystallized from ether to furnish an analytical sample reported in Table I. Yield, 30%.

Preparation of 2-Hydroxymethylene-7 α -alkylthiosteroids (IVa–IVg)—The 7 α -alkylthio-3-oxosteroid was treated with sodium hydride and ethyl formate in benzene solution under the similar conditions as those reported by Clinton, *et al.*⁴⁾ The resulting crude product was recrystallized from AcOEt or acetone to give the corresponding 2-hydroxymethylene-7 α -alkylthio steroid. Yield, 85–95%.

Preparation of 7 α -Alkylthio-5 α -androstan-3-one[3,2-*c*]pyrazoles (Va–Vg)—2-Hydroxymethylene-7 α -alkylthiosteroid was treated with hydrazine hydrate (80%) in EtOH under the similar condition as described in ref. 4. The resulting crude product was recrystallized from AcOEt to give a pure material. Yield, 80–90%. The results obtained by these procedures are shown in Table I.

Preparation of 7 α -Ethylsulfinyl and 7 α -Ethylsulfonylsteroids—Oxidation of IIc, IIIc and Vc with monoperphthalic acid (MPA) was each performed in the similar manner described by Schaub, *et al.*⁵⁾ The 7 α -ethylthiosteroid (3 millimoles) was dissolved in 20 ml of methylene chloride and 1.1 mole equivalents of ethereal MPA was then added. The reaction mixture was allowed to stand at room temperature for 24 hr and washed with 5% NaHCO₃, water, and dried. Evaporation of the solvent under reduced pressure gave a crystalline residue, which was recrystallized from the solvent (described below) to give the corresponding 7 α -ethylsulfinyl derivative. Yield, 40–50%.

The 7 α -ethylsulfinyl derivative (3 millimoles) was dissolved or suspended in 30 ml of methylene chloride and treated with 1.1 mole equivalents of ethereal MPA according to the procedure described for the preparation of 7 α -sulfinyl derivative. The compound obtained was recrystallized from the solvent (described below) to furnish the corresponding 7 α -ethylsulfonyl derivative. Yield, 70–80%.

The A-homo-oxasteroids were prepared by treatment with excess of ethereal MPA at room temperature for 4 days.

The compounds obtained by these procedures are summarized as follows:

a) 7 α -Ethylsulfinyl-17 β -hydroxy-17 α -methylandrosta-4-en-3-one (VIa): Recryst. from acetone-dichloroethane, mp 192–195° (decomp.), $[\alpha]_D^{25}$ –34.0° ($c=0.62$). UV λ_{max} m μ (ϵ): 234.5 (11600). IR ν_{max} cm^{–1}: 3510 (OH), 1662 (CO), 1620 (C=C). *Anal.* Calcd. for C₂₂H₃₄O₃S: C, 69.80; H, 9.13; S, 8.49. Found: C, 69.59; H, 9.13; S, 8.45.

b) 7 α -Ethylsulfonyl-17 β -hydroxy-17 α -methylandrosta-4-en-3-one (VIb): Recryst. from acetone, mp 151–153° (decomp.), $[\alpha]_D^{25}$ +5.5° ($c=0.61$), UV λ_{max} m μ (ϵ): 241.5 (15800). IR ν_{max} cm^{–1}: 3598 (OH), 1660 (CO), 1622 (C=C). *Anal.* Calcd. for C₂₂H₃₄O₄S: C, 66.97; H, 8.69; S, 8.13. Found: C, 66.93; H, 8.62; S, 8.12.

c) 7 α -Ethylsulfinyl-17 β -hydroxy-17 α -methylandrostan-3-one (VIIa): Recryst. from acetone, mp 219–221° (decomp.), $[\alpha]_D^{25}$ –75.0° ($c=0.51$). IR ν_{max} cm^{–1}: 3475 (OH), 1709 (CO). *Anal.* Calcd. for C₂₂H₃₆O₃S: C, 69.43; H, 9.54; S, 8.43. Found: C, 69.37; H, 9.57; S, 8.47.

d) 7 α -Ethylsulfonyl-17 β -hydroxy-17 α -methylandrostan-3-one (VIIb): Recryst. from acetone, mp 227–230° (decomp.), $[\alpha]_D^{25}$ +55.0° ($c=0.55$). IR ν_{max} cm^{–1}: 3610 (OH), 1712 (CO). *Anal.* Calcd. for C₂₂H₃₆O₄S: C, 66.62; H, 9.15; S, 8.09. Found: C, 66.24; H, 9.02; S, 8.20.

e) The Mixture of 7 α -ethylsulfonyl-17 β -hydroxy-17 α -methyl-A-homo-4-oxa-5 α -androstan-3-one (VIIIa) and 7 α -ethylsulfonyl-17 β -hydroxy-17 α -methyl-A-homo-3-oxa-5 α -androstan-4-one (VIIIb): Recryst. from acetone-ether, mp 239–241° (decomp.), IR ν_{max} cm^{–1}: 3450 (OH), 1735, 1710 (CO). *Anal.* Calcd. for C₂₃H₃₈O₅S: C, 64.06; H, 8.80; S, 7.77. Found: C, 64.00; H, 8.82; S, 7.99.

14) F.L. Weisenborn and H.E. Applegate, *J. Am. Chem. Soc.*, **81**, 1960 (1959).

15) R.E. Counsell, P.D. Klimstra, and F.B. Colton, *J. Org. Chem.*, **27**, 248 (1962).

f) 7 α -Ethylsulfinyl-17 β -hydroxy-17 α -methylandrostano[3,2-*c*]pyrazole (IXa): Recryst. from benzene, mp 174—178° (decomp.), $[\alpha]_D -55.0^\circ$ ($c=0.58$). UV $\lambda_{\max}$ m μ (ϵ): 223.5 (5400). IR $\nu_{\max}$ cm $^{-1}$: 3380, 3300 (OH, NH), 1630, 1597, 1560 (pyrazole ring). Anal. Calcd. for C₂₃H₃₆O₂N₂S: C, 68.27; H, 8.97; N, 6.93; S, 7.93. Found: C, 68.27; H, 8.99; N, 6.60; S, 7.68.

g) 7 α -Ethylsulfonyl-17 β -hydroxy-17 α -methylandrostano[3,2-*c*]pyrazole (IXb): Recryst. from acetone-benzene, mp 238—241° (decomp.), $[\alpha]_D -32.0^\circ$ ($c=0.65$). UV $\lambda_{\max}$ m μ (ϵ): 224 (4700). IR $\nu_{\max}$ cm $^{-1}$: 3380 (OH), 1630, 1598, 1569 (pyrazole ring). Anal. Calcd. for C₂₃H₃₆O₃N₂S: C, 65.68; H, 8.63; N, 6.66; S, 7.62. Found: C, 65.41; H, 8.63; N, 6.50; S, 7.38.

7 α -Ethylthio-17 β -hydroxy-17 α -methylandrostano[3,2-*c*]-5'-hydroxy- $\Delta^{2'}$ -isoxazoline (XIV) and 7 α -Ethylthio-17 β -hydroxy-17 α -methylandrostano[2,3-*d*]isoxazole (XVIII)—To a solution of 2-hydroxymethylene-7 α -ethylthio-17 β -hydroxy-17 α -methylandrostan-3-one (IVc) (3.0 g) in AcOH (60 ml) was added a solution of hydroxylamine hydrochloride (0.74 g) in water (12 ml). The solution was stirred at room temperature for 6 hr and allowed to stand overnight. The reaction mixture was diluted with water and extracted with AcOEt. The AcOEt extract was successively washed with water, 5% NaHCO₃, water and dried over Na₂SO₄. Evaporation of the solvent gave 3.25 g of an oily product, which was chromatographed on silica gel. The eluate with benzene-ether (9:1) afforded 2.64 g of crystalline product, which was recrystallized from hexane-ether to give needles of the [2,3-*d*]isoxazole (XVIII) (2.3 g), mp 141—145°, $[\alpha]_D -61.6^\circ$ ($c=0.92$). UV $\lambda_{\max}$ m μ (ϵ): 225 (9500). IR $\nu_{\max}$ cm $^{-1}$: 3410 (OH), 1643, 1616 (isoxazole ring). NMR¹⁶⁾ τ : 9.19 (19-H), 9.10 (18-H), 8.72 (17 α -CH₃), 8.72 (t, $J=7.0$, SCH₂CH₃), 8.53 (17 β -OH), 7.42 (q, $J=7.0$, SCH₂CH₃), 6.92 (7 β -H), 1.80 (3'-H). Anal. Calcd. for C₂₃H₃₅O₂NS: C, 70.90; H, 9.06; N, 3.60; S, 8.23. Found: C, 71.17; H, 9.25; N, 3.38; S, 8.22.

Further elution with benzene-ether (3:1) afforded 0.65 g of a crystalline product, mp 215—225° (decomp.), which was recrystallized repeatedly from AcOEt to yield the [3,2-*c*]- $\Delta^{2'}$ -isoxazoline (XIV) (0.47 g), mp 235—238° (decomp.), IR $\nu_{\max}$ cm $^{-1}$: 3400 (OH), 1643 (C=N). NMR τ : 9.12 (19-H in XIVb), 9.07 (19-H in XIVa), 4.55 (d, $J=2.0$, 5' α -H in XIVa), 4.39 (d, $J=7.0$, 5' β -H in XIVb) (in DMSO-*d*₆). The NMR spectrum of XIV indicated a mixture of the isomeric 5'-hydroxy steroids (ratio of XIVa-XIVb was 1:2).

7 α -Ethylthio-17 β -hydroxy-17 α -methylandrostano[3,2-*c*]-5'-hydroxy- $\Delta^{2'}$ -isoxazoline 5'-Acetate (XVIIb)—The [3,2-*c*]-5'-hydroxy- $\Delta^{2'}$ -isoxazoline (XIV) (0.5 g) was acetylated with Ac₂O (1 ml) and pyridine (10 ml) at room temperature for 15 hr, and diluted with water. The resulting precipitate was collected by filtration and dried. Repeated crystallization of the crude product from ether gave the [3,2-*c*]-5'- α -acetoxy- $\Delta^{2'}$ -isoxazoline (XVIIb) as colorless needles (0.1 g), mp 188—192°, $[\alpha]_D -67.5^\circ$ ($c=0.40$). IR $\nu_{\max}$ cm $^{-1}$: 3550 (OH), 1756 (CO), 1210 (OAc). NMR τ : 9.06 (19-H), 7.91 (OAc), 3.36 (d, $J=7.0$, 5' β -H). Anal. Calcd. for C₂₅H₃₉O₄NS: C, 66.78; H, 8.74; N, 3.12; S, 7.13. Found: C, 66.59; H, 8.74; N, 2.85; S, 7.00.

The NMR spectrum of the acetylation product (mp 168—175°) indicated a mixture being of the isomeric 5'-acetoxy derivatives (ratio of XVIIa-XVIIb was 5:6) as follows. NMR τ : 9.05 (19-H in XVIIb), 9.00 (19-H in XVIIa), 3.69 (d, $J=2.0$, 5' α -H in XVIIa), 3.36 (d, $J=7.0$, 5' β -H in XVIIb).

7 α -Ethylthio-17 β -hydroxy-17 α -methylandrostano[3,2-*c*]isoxazole (XVI)—A solution of the [3,2-*c*]isoxazoline (XIV) (0.4 g) in a mixture of AcOH (50 ml) and 9% HCl-ether (1 ml) was stirred at room temperature for 30 min. The reaction mixture was washed with 5% NaHCO₃, water and dried over Na₂SO₄. After evaporation of the extract, the resulting oily residue (0.45 g) was chromatographed on silica gel. The eluate with benzene, after recrystallization from ether, gave the [3,2-*c*]isoxazole (XVI) (0.30 g) as colorless prisms, mp 147—149°, $[\alpha]_D -56.6^\circ$ ($c=1.74$). UV $\lambda_{\max}$ m μ (ϵ): 224 (10100). IR $\nu_{\max}$ cm $^{-1}$: 3400 (OH), 1616 (C=N). NMR τ : 9.21 (19-H), 9.12 (18-H), 8.74 (17 α -CH₃), 8.74 (t, $J=7.0$, SCH₂CH₃), 8.51 (17 β -OH), 7.46 (q, $J=7.0$, SCH₂CH₃), 7.02 (7 β -H), 1.87 (5'-H). Anal. Calcd. for C₂₃H₃₅O₂NS: C, 70.90; H, 9.06; N, 3.60; S, 8.23. Found: C, 70.90; H, 9.04; N, 3.86; S, 8.19.

7 α -Ethylthio-3 β ,17 β -dihydroxy-17 α -methylandrostano[2,3-*d*]- $\Delta^{2'}$ -isoxazoline (XV)—To a solution of 2-hydroxymethylene-7 α -ethylthio-17 β -hydroxy-17 α -methylandrostan-3-one (IVc) (2.0 g) in EtOH (50 ml) was added a solution of hydroxylamine hydrochloride (0.39 g) and AcONa (0.4 g) in water (10 ml). The solution was refluxed for 4 hr and then concentrated to ca. 10 ml under reduced pressure. The cooled solution afforded 1.05 g of crystalline residue, which was acetylated with Ac₂O (2 ml) and pyridine (30 ml). Working up as usual way gave an oily residue, which was crystallized by trituration with benzene. The resulting precipitate was collected by filtration and recrystallized from AcOEt to give 0.25 g of the [2,3-*d*]isoxazoline (XV) as colorless needles, mp 184—187°, $[\alpha]_D -6.8^\circ$ ($c=0.91$). IR $\nu_{\max}$ cm $^{-1}$: 3300 (OH), 1623 (C=N). NMR τ : 9.27 (19-H), 9.22 (18-H), 8.95 (17 α -CH₃), 8.85 (t, $J=7.0$, SCH₂CH₃), 2.48 (d, $J=1.5$, 3'-H) (in DMSO-*d*₆). Anal. Calcd. for C₂₃H₃₇O₃NS: C, 67.77; H, 9.15; N, 3.34; S, 7.87. Found: C, 67.74; H, 9.36; N, 3.33; S, 7.74.

The residue from the filtrate (benzene solution) was chromatographed on silica gel. The eluate with benzene-ether (9:1) afforded 0.55 g of needles, mp 187—190°, which was identified 7 α -ethylthio-17 β -hydroxy-17 α -methylandrostano[3,2-*c*]-5'- α -hydroxy- $\Delta^{2'}$ -isoxazoline 5'-acetate (XVIIb) by mixture melting point and infrared spectrum.

16) Abbreviation used s=singlet, d=doublet, and q=quartet. Coupling constant J are given in cps.

Further eluate with benzene-ether (2:1) gave 0.05 g of additional the [2,3-*d*]isoxazoline (XV).

Acid Treatment of the [2,3-*d*]Isoxazoline (XV)—XV was treated with AcOH and 9% HCl-ether in the similar way as that in XIV. The crude product was recrystallized from ether-hexane to give a pure crystal, mp 139–143°, which was identical with the [2,3-*d*]isoxazole (XVIII) described above.

2 α -Cyano-7 α -ethylthio-17 β -hydroxy-17 α -methylandrostan-3-one (XIX)—To a solution of the [2,3-*d*]isoxazole (XVIII) (0.5 g) in anhyd. MeOH (5 ml) was added 0.5 g of MeONa. The mixture was stirred at room temperature for 3.5 hr. During this period, the sodium salt of the 2 α -cyano ketone precipitated from the solution. The reaction mixture was acidified with 5% HCl and diluted with water. The resulting precipitate was collected by filtration, washed with water and dried. Recrystallization from MeOH afforded 0.35 g of 2 α -cyano-3-oxosteroid (XIX), mp 218–227° (decomp.), $[\alpha]_D -61.6^\circ$ ($c=1.28$). UV λ_{max} m μ (ϵ): 233 (11900). IR ν_{max} cm $^{-1}$: 3400 (OH), 2200 (CN), 1730 ($>C=O$), 1659 (NC- $\dot{C}=C$ -OH). Anal. Calcd. for C₂₃H₃₅O₂NS: C, 70.90; H, 9.06; N, 3.60; S, 8.23. Found: C, 70.78; H, 9.03; N, 3.41; S, 8.09.

2-Hydroxyiminomethyl-3-hydroxyimino-7 α -ethylthio-17 α -methylandrostan-17 β -ol (XX)—To a solution of 2-hydroxymethylene-3-oxosteroid (IVc) (1.0 g) in pyridine (20 ml) was added a solution of hydroxylamine hydrochloride (1.23 g) in water (2 ml). The mixture solution was stirred at room temperature for 1.5 hr, and poured into water and extracted with AcOEt. Working up as usual gave 1.3 g of an oily residue, which was crystallized by trituration with benzene. The resulting crystalline product was collected by filtration and recrystallized from AcOEt to give the dioxime (XX) (0.53 g) as needles, mp 206–207°, $[\alpha]_D -143.5^\circ$ ($c=1.03$) (in dioxane). IR ν_{max} cm $^{-1}$: 3260 (OH), 1656 (C=N). NMR τ : 3.26 (d, $J=7.0$, CH=N), -0.51 , -0.64 (=NOH) (in DMSO- d_6). Anal. Calcd. for C₂₃H₃₃O₃N₂S: C, 75.36; H, 9.06; N, 6.63; S, 7.59. Found: C, 75.56; H, 8.90; N, 6.68; S, 7.77.

The residue from the filtrate (benzene solution) was chromatographed on silica gel and eluate with benzene-ether (4:1), after recrystallization from AcOEt, afforded 0.1 g of a pure material, mp 185–188°. This compound was proved to be identical with the [2,3-*d*]isoxazoline (XV) by mixed melting point and infrared spectrum.

17 β -Hydroxy-17 α -methylandrostan-3,2-*c*]-5'-hydroxy- Δ^2 '-isoxazoline (XI)—XI was prepared according to the method of Manson, *et al.*^{7a)} Repeated crystallization from AcOEt gave an analytical sample as colorless needles, mp 244–246° (lit.^{7a)} mp 233–237°. Its NMR spectrum showed a mixture being of 5' α and 5' β -epimers (ratio of 5' α -ol-5' β -ol was 2:1). NMR τ : 9.16 (19-H in the 5' α -ol), 9.12 (19-H in the 5' β -ol), 4.60 (d, $J=2.0$, 5' α -H in the 5' β -ol), 4.39 (d, $J=7.0$, 5' β -H in the 5' α -ol) (in DMSO- d_6). Anal. Calcd. for C₂₁H₃₃O₃N: C, 72.18; H, 9.58; N, 4.03. Found: C, 72.86; H, 9.64; N, 4.26.

The NMR spectrum of the acetylation product of XI showed a mixture of the isomeric 5'-acetoxy isoxazolines (ratio of 5' α -acetate-5' β -acetate was 3:5) as follows. NMR τ : 9.08 (19-H in the 5' α -acetate), 9.03 (19-H in the 5' β -acetate), 3.69 (d, $J=2.0$, 5' α -H in the 5' β -acetate), 3.36 (d, $J=7.0$, 5' β -H in the 5' α -acetate).

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