deeply, the thiourea began to solidify as a compact, solid mass. Purification by recrystallization from dil. MeOH yielded between 70 % and 80 % of the theoretical amount.

Synthesis of N-Alkyl-4-morpholinecarboxamidine Sulfate——A mixture of 0.1 mole of N-alkyl-4-morpholinethiocarboxamide and 6.4 g. (0.05 mole) of Me_2SO_4 was refluxed at 110° in an oil bath for 1 hr. The S-methylisothiourea sulfate was then dissolved in 20 cc. of water, and cleared with charcoal. To the filtrate was added, all at once, 20 cc. of NH_3-water. Under agitation, the solution was gently warmed on a water bath over 3 hr. After a great part of MeSH was evolved, the solution was boiled, discolored with charcoal, and then concentrated under reduced pressure until it was anhydrous. The syrupy residue was covered with a layer of dry Me_2CO or anhyd. MeOH, and chilled for several days, whereupon it set to crystallize.

Summary

The eight compounds of N-alkyl-4-morpholinecarboxamidine sulfate were synthesized *via* N-alkyl-4-morpholinethiocarboxamide from alkyl isothiocyanate, wherein alkyl group stands for H, CH_3, C_2H_5, C_3H_7, C_4H_9, C_5H_{11}, C_6H_{13}, or cyclohexyl.

Any of the compounds synthesized was found inactive on any of polio, measles and influenza virus.

(Received July 23, 1962)

UDC 547.92:577.176.3

106. Keiichi Takamura, Chifuyu Isono, Sakae Takaku, and Yoshihiro Nitta :

Studies on Steroids. I. The Preparation and Properties of 17β-(N-Substituted 2-Amino-4-thiazolyl)-androst-4-en-3-one Series.

(*Research Laboratory, Chugai Pharmaceutical Co., Ltd.*[*1])

At the time of this investigation it had already been shown that modification of 17-position of androstane could give a various biological activity. Recently, Ralls and his co-workers[1)] described on the synthesis of 17β-(2-substituted 4-thiazolyl)androst-4-en-3-one series possessing pharmacological activity as cardiac glucoside. On the other hand, Schaub, *et al.*[2)] also reported on the synthesis of 17β-(2-amino-4-thiazolyl)androst-4-en-3-one series having no significant activity. The present authors attempted to prepare a various kinds of 17β-(N-substituted 2-amino-4-thiazolyl)androst-4-en-3-one series in order to examine the structure-activity relationships.

Synthesis of 17β-(2-alkylamino-(or 2-arylamino- or 2-N,N-alkylarylamino-)-4-thiazolyl)-androst-4-en-3-one Series

21 Mesylates (II) of Reichstein's compound S, cortisone and desoxycorticosterone, were prepared by treatment of the parent compounds with methanesulfonyl chloride in pyridine at low temperature respectively.

The conversion of II to 21-iodides derivatives (III) were carried out with use of sodium iodide in acetone. 21-Iodides (III) were condensed with thiourea, N-alkylthiourea

---

*1 Takadaminami-cho, Toshima-ku, Tokyo (高村圭一, 磯野千冬, 高久 栄, 新田義博).

1) J. W. Ralls, M. Grove, C. G. Bergstrom : U. S. Pat. 2,793,207 (1957).

2) R. E. Schaub, M. J. Weiss : J. Org. Chem., **26**, 1223 (1961).

or 2-N,N-alkylarylthiourea in acetone to give the corresponding 17β-(2-amino-(or 2-N-alkylamino- or 2-arylamino- or 2-N,N-alkylarylamino-)-4-thiazolyl)androst-4-en-3-one hydroiodides (IV).

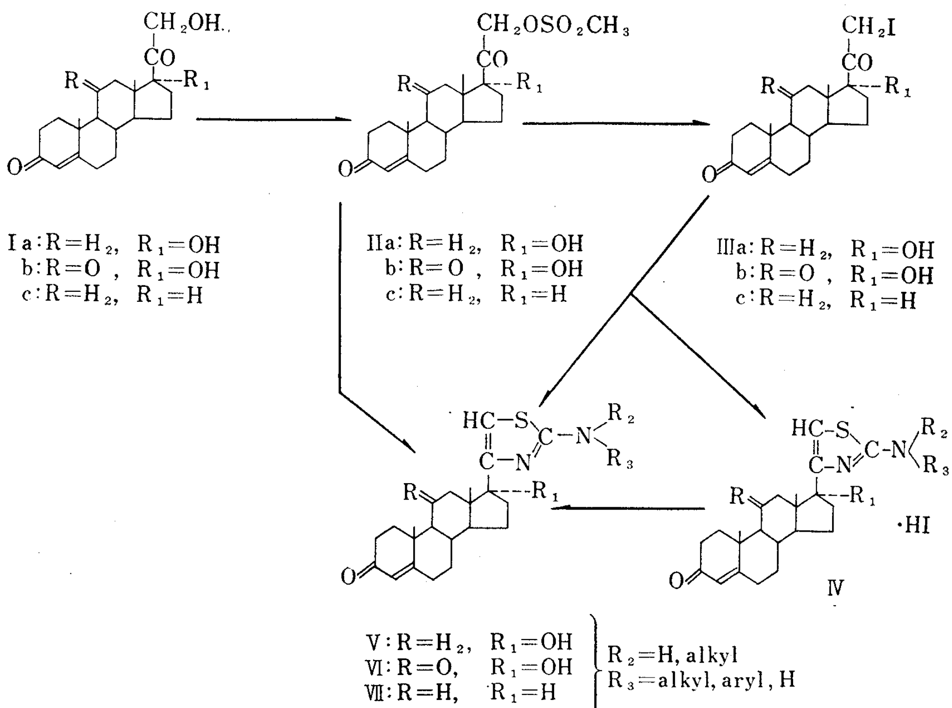
17β-(2-amino-(or 2-alkylamino- or 2-arylamino- or 2-N,N-alkylarylamino-)-4-thiazolyl)androst-4-en-3-one (V～VII) were obtained in excellent yield by treatment of IV with sodium bicarbonate under an atmosphere of nitrogen.

These compounds (V～VII) were also obtained in excellent yield by condensation of 21-iodide (III) with thiourea, a various N-alkylthiourea, N-arylthiourea or N,N-alkylarylthiourea in the presence of basic catalyst such as, sodium bicarbonate, potassium bicarbonate, sodium carbonate, sodium acetate or sodium hydroxide in boiling acetone under a current of nitrogen. The physical constant of the compounds are listed in Table I.

Schaub, *et al.*[2] also reported the preparation of 17β-(2-amino-4-thiazolyl)androst-4-en-3-one series from 21-tosylates of corticoid steroids by refluxing with thiourea in ethanol.

The author's attempt to prepare 17β-(2-amino-4-thiazolyl)androst-4-en-3-one derivatives by the condensation of 21-mesylate (II) with thiourea according to the above condition was unsuccessful.

However, 17β-(2-amino-(or 2-N-alkylamino-)-4-thiazolyl)androst-4-en-3-one series (V) was obtained by the condensation of II with thiourea in anhydrous dimethylformamide, followed by treatment of the reaction mixture with sodium bicarbonate under an atmosphere of nitrogen and the purification by chromatography through florisil. These synthesis sheet was illustrated in Chart 1.



Ia: $R=H_2$, $R_1=OH$
b: $R=O$, $R_1=OH$
c: $R=H_2$, $R_1=H$

IIa: $R=H_2$, $R_1=OH$
b: $R=O$, $R_1=OH$
c: $R=H_2$, $R_1=H$

IIIa: $R=H_2$, $R_1=OH$
b: $R=O$, $R_1=OH$
c: $R=H_2$, $R_1=H$

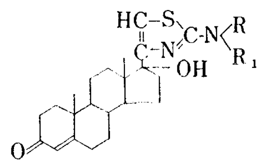
IV

V: $R=H_2$, $R_1=OH$
VI: $R=O$, $R_1=OH$
VII: $R=H$, $R_1=H$
R_2=H, alkyl
R_3=alkyl, aryl, H

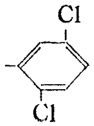
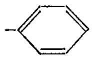
Chart 1.

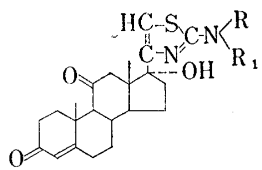
Ultraviolet spectra of these compounds (V～VII) have an absorption maximum in the range of 239～245 mμ due to Δ^4-3-keto group. These compouds (V～VII) were substantiated by examination of the infrared spectra which showed disappearance of the 20-carbonyl band at 1710 cm^{-1} and the presence of strong absorption near 1590～1500 cm^{-1} due to thiazol ring. The 2-alkylamino-4-thiazolyl derivatives of V～VII were

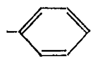
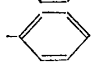
TABLE I.

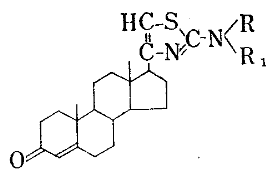


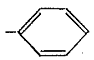
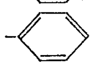
Compound	R	R_1	m.p. (b.p. °C)	Formula	Analyses (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Yield (%)	$[\alpha]_D^{CHCl_3}$	λ_{max}^{EtOH} mμ (log ε)
Va	H	H	226.0	$C_{22}H_{30}O_2N_2S_1$	68.35	7.82	7.24	68.43	7.99	7.39	94.4	+ 61.69 (c=0.2378)	242.5~245 (4.24)
Vb	H	CH_3	227.0	$C_{23}H_{32}O_2N_2S_1$	68.97	8.05	7.00	68.86	8.12	6.88	97.5	+105.4 (c=0.8126)	243.2~244.3 (4.30)
Vc	H	C_2H_5	211.0	$C_{24}H_{34}O_2N_2S_1$	69.57	8.21	6.76	69.63	8.39	6.76	88.7	+102.0 (c=0.9831)	242.5~244.5 (4.09)
Vd	H	C_3H_7	184.0	$C_{25}H_{36}O_2N_2S_1$	70.09	8.41	6.54	69.74	8.36	6.68	92.8	+105.2 (c=1.077)	242.3~245 (4.07)
Ve	H	iso-C_3H_7	187.5	$C_{25}H_{36}O_2N_2S_1$	70.09	8.41	6.54	69.97	8.55	6.43	92.8	+109.9 (c=1.0159)	242.3~245 (4.29)
Vf	H	C_4H_9	153.5	$C_{26}H_{38}O_2N_2S_1$	70.59	8.59	6.33	70.59	8.62	6.47	96.5	+ 96.4 (c=1.0195)	241.5~243.5 (4.32)
Vg	H	*sec*-C_4H_9	139.0	$C_{26}H_{38}O_2N_2S_1$	70.59	8.59	6.33	70.28	8.75	6.49	89.6	+100.5 (c=0.932)	243.2~244.2 (4.29)
Vh	H	$-C_6H_5$	247.0	$C_{28}H_{34}O_2N_2S_1$	72.69	7.40	6.05	72.74	7.57	6.35	96.1	+ 98.0 (c=0.400)	239.8~242 (4.21) 289 ~292 (4.20)
Vi	H	$-C_6H_4-OCH_3$ (p)	195.0	$C_{29}H_{36}O_3N_2S_1$	70.73	7.32	5.69	70.94	7.43	5.37	92.5	+103.4 (c=0.847)	241.5~242.5 (4.28) 296 (4.25)
Vj	H	$-C_6H_4-OC_2H_5$ (p)	185.0	$C_{30}H_{38}O_3N_2S_1$	71.15	7.51	5.53	70.88	7.81	5.51	92.5	+100.2 (c=0.600)	241 ~242.5 (4.24) 296 ~298 (4.22)
Vk	H	$-C_6H_4-CH_3$ (p)	217.0	$C_{29}H_{36}O_2N_2S_1$	73.07	7.61	5.87	73.29	7.85	6.05	89.7	+102.4 (c=0.629)	240 ~242 (4.16) 293 ~296 (4.25)
Vl	H	$-C_6H_4-CH_3$ (o)	213.5	$C_{29}H_{36}O_2N_2S_1$	73.07	7.61	5.87	73.13	7.85	5.65	83.3	+102.4 (c=0.688)	240 ~242.5 (4.10) 293 ~296 (3.87)
Vm	H	$-C_6H_4-Cl$ (p)	202	$C_{28}H_{33}O_2N_2S_1Cl_1$	67.67	6.65	5.67	67.95	6.88	5.43	85.5	+ 81.1 (c=0.073)[a]	239.8~241.8 (4.16) 297 ~300 (4.29)
Vn	H	$-C_6H_4-Cl$ (o)	210	$C_{28}H_{33}O_2N_2S_1Cl_1$	67.67	6.65	5.67	67.92	6.65	5.62	98.1	+ 58.1 (c=0.206)[a]	238.5~241.5 (4.16) 293 ~295.5 (4.07)
Vo	H	$-C_6H_4-Cl$ (m)	204	$C_{28}H_{33}O_2N_2S_1Cl_1$	67.67	6.65	5.67	67.78	6.91	5.89	92.0	+131.1 (c=0.240)[a]	240.5~242.5 (3.85) 296 ~298 (3.89)
Vp	H	$-C_6H_3-Cl_2$ (2,3)	243	$C_{28}H_{32}O_2N_2S_1Cl_2$	63.28	6.03	5.27	63.56	6.05	5.49	86.2	+ 81.8 (c=0.397)[a]	236 ~237 (3.97) 296 ~299 (3.89)

Vq	H		223	$C_{28}H_{33}O_2N_2S_1Cl_2$	63.28	6.03	5.27	63.48	6.26	5.12	95.6	+102.6 (c=0.336)[a]	236.5～238.5 (4.05) 293.5～295.5 (3.95)
Vr	CH_3		185	$C_{29}H_{36}O_2N_2S_1$	73.44	7.81	5.71	73.29	7.72	5.72	96.1	+109.0 (c=0.785)	240.5～242.5 (4.40) 295 (3.99)
Vs	C_2H_5		151	$C_{30}H_{38}O_2N_2S_1$	73.08	7.61	5.88	73.32	7.73	5.97	96.2	+114.5 (c=1.612)	239.3～241.8 (4.41) 295 ～296 (4.41)
Vt	H		219	$C_{28}H_{40}O_2N_2S_1$	71.76	8.60	5.98	71.72	8.65	5.99	83.5	+ 79.0 (c=0.3275)	242.0～244.0 (4.25)



VIa	H	H	250	$C_{22}H_{28}O_3N_2S_1$	65.98	7.05	7.00	66.25	7.23	7.36	91.0	+163.1 (c=0.309)	240.5～242 (4.35)
VIb	H	CH_3	243	$C_{23}H_{30}O_3N_2S_1$	66.64	7.30	6.78	66.39	7.70	6.87	90.0	+171.6 (c=0.802)	239 (4.26)
VIc	H		247	$C_{29}H_{24}O_3N_2S_1$	70.57	6.77	5.88	70.60	6.47	5.98	89.0	+ 11.7 (c=0.323)	264 (3.77)
VId	CH_3		214	$C_{30}H_{36}O_3N_2S_1$	71.00	6.99	5.71	70.97	6.88	5.48	86.5	+141.0 (c=1.031)	241.5 (4.37) 295 ～296 (3.79)



VIIa	H	CH_3	219	$C_{23}H_{32}ON_2S_1$	71.84	8.39	7.29	72.00	8.54	7.24	83.9	+132.7 (c=0.662)	242.5 (4.24)
VIIb	H		226	$C_{29}H_{36}ON_2S_1$	75.30	7.67	6.27	75.40	7.76	6.21	81.8	+111.4 (c=0.984)	241 ～243 (4.16) 295 ～298 (3.65)
VIIc	C_2H_5		144	$C_{31}H_{40}ON_2S_1$	75.91	8.08	5.90	76.07	8.13	6.05	93.1	+123.5 (c=0.945)	241 ～242 (4.51) 296 ～299 (3.99)

a) NN-dimethylformamide.

TABLE II. Infrared Absorption of V～VII (KBr disk) (cm^{-1})

Compound cm^{-1}	ν_{OH} (17-OH)	ν_{N-H} $\nu_{as\,N-H}$	$\nu_{s\,N-H}$	Overton of ν_{C-H} benzene		ν_{C-H} $\nu_{as\,C-H}$	$\nu_{s\,C-H}$	$\nu_{C=O}$ (Δ^4 3C=O)	δ_{N-H}	$\nu_{C=C}$	II band of thiazol ring	Benzene ring		δ_{C-H} (benzene)		
Va	3507 s	3342 s	3257 s			2937 s	2862 s	1665 s	1650 s	1620 w	1511 s					
Vb	3502 s	3367 s				2927 s	2862 s	1664 s		1610 w	1540 s					
Vc	3522 s	3367 s				2942 s	2877 s	1662 s		1610 w	1540 s					
Vd	3520 s	3372 s				2937 s	2872 s	1671 s		1612 w	1558 s					
Ve	3514 s	3369 s				2979～2949 s	2884～2871 s	1649 s		1615 w	1541 s					
Vf	3472m	3327 s				2947 s	2927 s	1665 s		1607 w	1570 s					
Vg	3425m	3325 s				2935 s	2870 s	1661 s		1611m	1563 s					
Vh	3552m	3322 s		3177 w	3107 w	2977 s	2857 s	1667 s		1606m	1557 s	1500 s		757m	721m	monosubstituted benzene
Vi	3513 s	3463～3367 s		3200m		2930 s	2867 s	1658 s		1610m	1550 s	1562 s	1510 s	794m		*p*-substituted benzene
Vj	3495 s	3490 s		3105m		2940 s	2865 s	1665 s		1613m	1536 s	1551 s	1531 s	824m		〃
Vk	3537m	3377～3322m		3122 w	3022 w	2932 s	2867 s	1664 s		1613m	1550 s	1592 s	1538 s	821m		〃
Vl	3527m	3327m		3127 w	3027 w	2937 s	2887 s	1660 s		1610m	1540m	1598 s	1514 s	751m		*o*-substituted benzene
Vm	3500m	3300m		3190 w	3080 w	2900 s	2809m	1650 s		1605m	1530 s	1490 s		826m		*p*-substituted benzene
Vn	3500m	3420～3330m		3042 w	3020 w	2925 s	2875m	1634 s		1606m	1530 s	1600 s	1525 s	754m		*o*-substituted benzene
Vo	3515m	3295 s		3180m	3080m	2910 s	2860 s	1662 s		1598 w	1531 s	1547 s	1514 s	775m	723m	*m*-substituted benzene
Vp	3535～3460m	3330m		3095 w	3025 w	2925 s	2880 s	1664 s		1607 w	1520 s	1590 s	1515 s	780m		1,2,3-substituted benzene
Vq	3617～3427m	3277m		3107 w	3022 w	2937 s	2882 s	1667 s		1610 w	1530 s	1595 s	1507 s	801m		1,2,5-substituted benzene
Vr	3570～3460m					2925 s	2870 s	1680 s		1615 w	1520 s	1495 s		769m	702m	monosubstituted benzene
Vs	3360m			3102 w		2925 s	2858 s	1665 s		1615 w	1585 s	1595 s	1515 s	765m	697m	〃
Vt	3200m					2930 s	2885 s	1665 s		1617 w	1550 s					

Compound cm^{-1}	ν_{O-H} (17-OH)	ν_{N-H} $\nu_{as\,N-H}$	$\nu_{s\,N-H}$	Overton of ν_{C-H} benzene		ν_{C-H} $\nu_{as\,C-H}$	$\nu_{s\,C-H}$	$\nu_{C=O}$ (11-C=O)	(Δ 3C=O)	δ_{N-H}	$\nu_{C=C}$ (Δ^4)	II band of thiazol ring	Benzene ring		ν_{C-H} (benzene)		
VIa	3455m	3200 s	3130 s			2945 s	2875 s	1700 s	1661 s	1641 s	1616 w	1532 s					
VIb	3480m	3280 s				2940 s	2880 s	1700 s	1670 s		1617 w	1585 s					
VIc	3502m	3280 s		3128 w	3087 w	2980 s	2870 s	1703 s	1662 s		1600 w	1553 s	1563m	1533 s	752 s	715 s	monosubstituted benzene
VId	3409m					2948 s	2880 s	1696 s	1648 s		1601 w	1535 s	1586m	1517m	769 s	697 s	〃
VIIa		3315 s				2940 s	2875 s		1660 s		1611 w	1550 s					
VIIb		3306 s		3200 w	3120～3020 w	2935 s	2870 s		1660 s		1604 s	1550～1530 s	1604 s	1498 s	745 s	689 s	〃
VIIc				3122 w		2935 s	2880 s		1669 s		1611 w	1586m	1598 s	1513 s	767 s	697 s	〃

s : strong m : medium w : weak

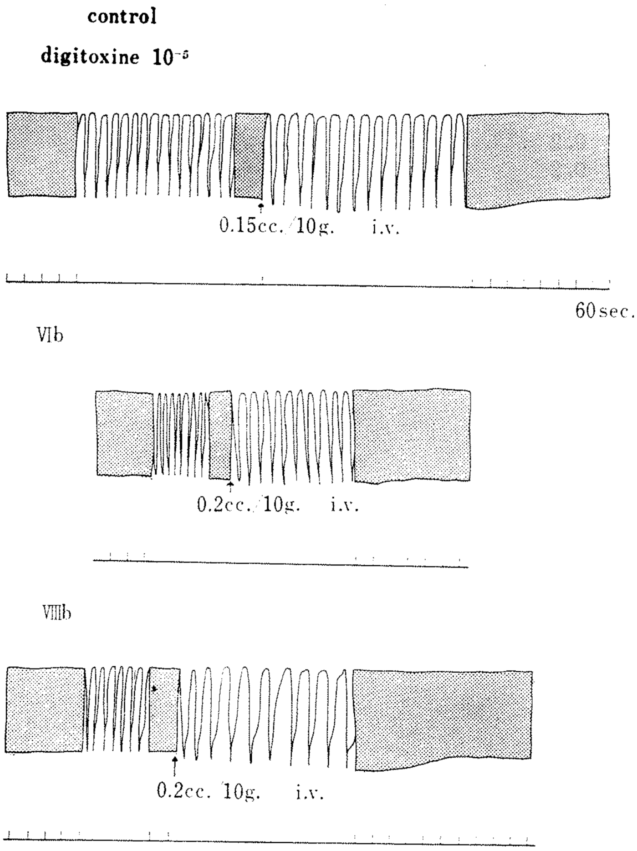


Fig. 1. The Changes of Contractile Force of Isolated Frog Heart

TABLE III. Toxicity by Pigeon and Frog method

No.	Pigeon LD mg./kg.	Frog LD mg./g. after 4 hr.	Frog LD mg./g. after 12 hr.
Digitoxin	0.60	0.001	0.001
Gitoxin	1.21		
Digoxin	0.45	0.001	0.001
Va	11.30	0.030[a]	0.030[a]
Vb	6.00	0.030[a]	0.030[a]
Vc	5.80	0.030	0.030
Vd	16.70	0.030[a]	0.030[a]
Ve	5.33	0.030[a]	0.030[a]
Vf	16.70	0.030[a]	0.030[a]
Vg	18.70	0.030[a]	0.030[a]
Vh	4.67	0.030[a]	0.030[a]
Vi		0.030 1/3[b]	0.030 1/3[b]
Vj	10.70		
Vk	9.70	0.030[a]	0.030[a]
Vl	7.00	0.030[a]	0.030[a]
Vr	5.20	0.030[a]	0.030[a]
Vs	4.70	0.030[a]	0.030[a]
Vt		0.060 1/3[b]	0.060
VIa	15.30	0.030 1/3[b]	0.030 1/3[b]
VIb	16.00	0.028	0.028
VIc		0.030[a]	0.030[a]
VId	12.70	0.030	0.030
VIIa	7.10	0.030	0.030
VIIb	2.15	0.030 1/3[b]	0.030 1/3[b]
VIIc	4.70	0.030 1/3[b]	0.030 1/3[b]

a) This indicates that the animals did not die until each dose was injected.
b) killed animals/treated animals.

Table IV. Effect on Isolated Frog Heart of Compounds

No.	Concentration	Dose cc./10 g.	Contractile Force inhibit — increase +	Heart Rate diminish — increase +
Va	10^{-4}	0.2	—	—
	$10^{-4}\times 2.5$	0.2	—	—
Vb	10^{-4}	0.2	+	—
Vc	$10^{-2}\times 5$	0.2		
	$10^{-3}\times 5$	0.05	±	—
	10^{-4}	0.2	+	—
	$10^{-4}\times 2.5$	0.05	—	±
	$10^{-4}\times 2.5$	0.1	—	—
	$10^{-4}\times 2.5$	0.2	—	—
Vd	10^{-4}	0.1	±	
	10^{-4}	0.2	±	
Ve	10^{-4}	0.2	—	
	10^{-4}	0.3	—	
Vf	10^{-4}	0.1	—	—
	10^{-4}	0.2	—2	—2
	$10^{-4}\times 2$	0.2	+	—
Vg	10^{-4}	0.1	—	
	10^{-4}	0.2	±	
Vh	10^{-4}	0.05	no effect	no effect
	10^{-4}	0.2	—	—
Vi	10^{-4}	0.05	no effect	no effect
	10^{-4}	0.2	no effect	no effect
Vk	10^{-4}	0.05	no effect	—
	10^{-4}	0.2		
	$10^{-4}\times 5$	0.2	no effect	no effect
	$10^{-4}\times 5$	0.2	+	—
Vl	10^{-4}	0.1	—	—
	10^{-4}	0.2	—	—
Vr	10^{-4}	0.2	no effect	no effect
Vs	10^{-4}	0.1	—	—
	10^{-4}	0.2	—	—
VIb	$10^{-3}\times 5$	0.05	+	
	$10^{-3}\times 5$	0.2	no effect	—
	10^{-4}	0.05	no effect	—
	10^{-4}	0.1	+ weak	
	10^{-4}	0.1	±	—
	10^{-4}	0.2	+	—
	10^{-4}	0.2	+	—
	10^{-4}	0.2	no effect	—
	10^{-4}	0.55 cc./body	+	
	$10^{-4}\times 2.5$	0.05	±	
	$10^{-4}\times 2.3$	0.1	no effect	—
	$10^{-4}\times 2.5$	0.2	no effect	—
VIIa	10^{-3}	0.2	—	
VIIb	10^{-4}	0.2	+	—
	10^{-4}	0.3	—	—
VIIc	10^{-4}	0.2		
	10^{-4}	0.2	—	—2
	$10^{-4}\times 2$	0.2	+	

confirmed by examination of infrared spectra which showed an absorption band near 3500 cm^{-1} due to N-H stretching, whereas the 2-N,N-alkylarylamino-4-thiazolyl derivatives of V～VIII did not show the corresponding absorption in the region. Furthermore, the 2-arylamino-4-thiazolyl derivatives of V～VIII showed absorption band near 290 mμ in the ultraviolet spectrum due to benzene ring and absorption band near 1595～1520 cm^{-1} and near 826～697 cm^{-1} due to substituted benzene. Infrared data of V～VIII are summarized in Table II.

Pharmacological Test

Screening tests of the compounds described above, were determined on the toxicity of pigeon method and the contractile force of isolated frog heart (Engelmann's test).

The compounds were compared with cardiac aglycone by using these test, as shown in Table III, and IV and in Fig. 1.

Toxicity of the compounds determined by pigeon method was compared with that of cardiac aglycone and these results indicated that their toxicity is lower than that of cardiac aglycone, as shown in Table III.

As shown in Fig. 1, it was indicated that the patterns of the compounds in Engelmann's test are same as that of cardiac aglycone.

As can be seen in Table III and IV, these compounds are believed to possess cardiac aglycone-like properties in pigeon method and Engelmann's test.

Experimental

Reichstein's Compound S 21-Mesylate (IIa)——A solution of 1 g. of Reichstein's compound S in a mixture of 5 cc. of pyridine and 1 cc. of methanesulfonyl chloride was allowed to stand overnight at 0～5°.

The reaction mixture was poured slowly, with stirring, into ice water. The precipitate thereby obtained was collected on a filter, washed with water, and recrystallized from MeOH gave colorless crystals, m.p. 184°(decomp.), yield, 74.5% (800 mg.). UV λ_{max}^{EtOH}: 240 mμ. $[\alpha]_D^{25}$ +120° (c=0.242, EtOH). IR λ_{max}^{KBr} cm^{-1}: 1750, 1670, 1610, 1360, 1170. *Anal.* Calcd. for $C_{22}H_{32}O_6S$: C, 62.25; H, 7.68. Found: C, 62.27; H, 7.55.

Cortison 21-Mesylate (IIb)——Treatment of 5 g. of cortisone in 22.7 cc. of pyridine with 5.7 g. of methanesulfonyl chloride, as described above for the preparation of cortisone 21-mesylate (IIb) afforded 4 g. (74%) of product, m.p. 192° (decomp.). *Anal.* Calcd. for $C_{22}H_{30}O_7S$: C, 60.27; H, 6.84. Found: C, 58.24; H, 7.45.

Desoxycorticosterone 21-Mesylate (IIc)——Treatment of 5 g. of desoxycorticosterone in 30 cc. of pyridine with 14 g. of methanesulfonyl chloride, as described above for the preparation of desoxycorticosterone 21-mesylate (IIc) afforded 3.5 g. product, m.p. 200～201° (decomp.).

Reichstein's Compound S 21-Iodide (IIIa)——To a solution of 3 g. of IIa in 50 cc. of Me_2CO was added 2.6 g. of NaI. After a few min., sodium mesylate began to separate. The mixture was refluxed for 30 min., and sodium mesylate was filtered, Me_2CO was removed from the both under reduced pressure, the residue was washed with water, and afforded yellow crystals, m.p. 151.5° (decomp.). Yield, 87% (2.8 g.). *Anal.* Calcd. for $C_{21}H_{29}O_3I$: C, 55.26; H, 6.45. Found: C, 55.34, H, 6.54.

Cortisone 21-Iodide (IIIb)——Treatment of 4 g. of IIb in 118 cc. of Me_2CO with 1.9 g. of NaI, as described above for the preparation of cortisone 21-iodide afforded 2.7 g. (78.7%) of product, m.p. 190° (decomp.).

Desoxycorticosterone 21-Iodide (IIIc)——Treatment of 3.5 g. of IIc in 100 cc. of Me_2CO with 2.5 g. of NaI, as described above for the preparation of IIIc afforded 2.7 g. (71.6%) of product, m.p. 125° (decomp.).

17α-Hydroxy-17β-(2-amino-4-thiazolyl)androst-4-en-3-one Hydroiodide (IV)——A solution of 1 g. of IIIa in 50 cc. of Me_2CO was added 0.3 g. of thiourea. The mixture was refluxed under an atmosphere of N_2 for 2 hr. The crystalline material that separated was collected and washed several times with Me_2CO and recrystallized from MeOH-Me_2CO (2:1) afforded colorless crystals, m.p. 240° (decomp.). Yield, 1.1 g. (98%). *Anal.* Calcd. for $C_{22}H_{31}O_2N_2S_1I$: C, 51.36; H, 6.03; N, 5.24. Found: C, 51.18; H, 6.01; N, 5.35.

17α-Hydroxy-17β-(2-amino-4-thiazolyl)androst-4-en-3-one (Va)——A solution of 1 g. IV in 100 cc. of 70% MeOH containing 1% $NaHCO_3$ was refluxed under an atmosphere of N_2 for 1 hr.

The resulting mixture was concentrated to a small volume and was added a small amount of water, a crystalline began to separate.

The cooled solution was filtered to give 0.73 g. (97.3%).

Recrystallization from EtOH gave white crystals, m.p. 226°(decomp.). λ_{max}^{EtOH} : 242.5～245 mμ (log ε 4.24). *Anal.* Calcd. for $C_{22}H_{30}O_2N_2S_1$: C, 68.35; H, 7.82; N, 7.24. Found : C, 68.43; H, 7.99; N, 7.39.

17β-(2-Alkylamino-(or 2-arylamino- or 2-N,N-alkylarylamino-)-4-thiazolyl)androst-4-en Series (V～VII)——To a solution of 0.01 mol of Ⅲa～c and 0.012 mol of N-substituted thiourea or N,N-disubstituted thiourea in 40 cc. of Me_2CO was added a solution 0.012 mole of basic catalyst such as, $NaHCO_3$, $KHCO_3$, NaOH, Na_2CO_3, NaOAc. The mixture was refluxed under an atmosphere of N_2 for 2 hr. and then concentrated to a small volume and chilled. The resulting mixture was filtered to give crystals. Recrystallization from EtOH gave crystals. Yield, 80～90%.

Va from IIa with Thiourea——A solution of 5 g. of Ⅱa and 1.5 g. of thiourea in 50 cc. of dry dimethylformamide was refluxed under an atomosphere of N_2 for 3 hr. The resulting mixture was concentrated to dryness under a reduced presure.

This was dissolved in dry $CHCl_3$, chromatographed through silica gel, eluted with $CHCl_3$ and a mixture of $CHCl_3$-MeOH (1:1), from the $CHCl_3$ layer, 3.3 g. of 17α-hydroxy-17β-(2-amino-4-thiazolyl)-androst-4-en-3-one methansulfonate was obtained Ⅳ m.p. 265°(decomp.).

To a solution of 3.3 g. of Ⅳ in 50 cc. of 70% MeOH containing 1% $NaHCO_3$ was refluxed under an atmosphere of N_2 for 1 hr. was distilled off, and the residue was recrystallized from EtOH. M.p. 226° (decomp.). Yield, 90% (2.3 g.). The IR of this products were essentially identical of Ⅴa.

The authors express their deep gratitude to Dr. S. Hayashi, Managing Director of this Company, and Mr. G. Tatsui, Director of this Laboratory, for their kind encouragement.

Thanks are also due to Mr. N. Ogikubo and Miss R. Tomii for ultraviolet and infrared spectral measurements, and Miss M. Ishii and Miss M. Oikawa for carrying out in microanalyses.

Summary

17β-(2-alkylamino-(or 2-arylamino- or 2-N,N-alkylarylamino-)-4-thiazolyl)androst-4-en-3-one derivatives were prepared from Reichstein's compound S 21-iodide, cortisone 21-iodide and desoxycorticosterone 21-iodide or corresponding 21-mesylate with N-alkylthiourea, N-arylthiourea or N,N-alkylarylthiourea respectively.

Some of these compounds were found to have a digitalis-like properties (cardiac glucoside properties) as a result of pharmacological test.

(Received August 29, 1962)