Panayotis Catsoulacos and Dimitrios Kallias

Department of Chemistry, Nuclear Research Center "Demokritos", Aghia Paraskevi Attikis, Athens, Greece

Received December 18, 1978

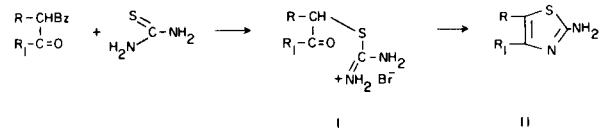
The treatment of 16α-bromo-17-ketosteroids and 2-bromo-3-ketosteroids with thiourea in dimethylformamide give the corresponding 2′-formamidothiazolosteroids.

The resulting 2′-formamidothiazoles were identical with those obtained in a similar reaction from 17β-bromo-16α,17α-oxidoandrostane with thiourea. Hydrolysis of the 2′-formamidothiazolosteroids led to the corresponding 2′-aminothiazoles, which also resulted from the interaction of bromoketones and thiourea in isopropanol.

The title compounds prepared were substantiated by examination of infrared, ultraviolet, mass and nuclear magnetic resonance spectra.

J. Heterocyclic Chem., **16**, 763 (1979).

Compounds with a condensed thiazole ring in different positions on a steroid molecule are synthesized by the well studied Hantzsch reaction (1). This reaction of an α-halocarbonyl compound with thiourea involves as the first step, the elimination of hydrogen halide and the formation of the acyclic intermediate (I), which cyclizes under drastic conditions to give the aminothiazole (II).



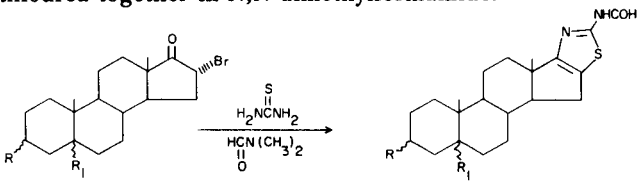
I II

Aminothiazole derivatives of steroids are well known as useful antagonists to hormonal substances (2), as agents which lower the blood pressure of mammals (3), as cardiotonotic and hypertensive agents (4-6), which regulate the cardiovascular system (7), for their digitalis regulating effect on cardiac arrhythmia (8), for their antiprogesterone activity (9), and for their usefulness in the treatment of hypophysis overloaded (10).

In continuation of our studies on the chemistry of heterocyclic steroidal compounds (11), we investigated the synthesis of 2′-aminothiazolo[5′,4′:16,17]- and 2′-aminothiazolo[5′,4′:2,3]steroids. Various workers (12,13) have prepared aminothiazole rings attached to the D-ring of the steroid molecule by the treatment of 16-bromo-17-ketosteroids with thiourea in ethanol under refluxing for 27 hours. In the present communication we describe the synthesis of various aminothiazolosteroids for the purpose of correlating pharmacological activity to chemical structure. The compounds prepared in this study are divided into three classes depending on the site of the thiazole ring fusion on the steroid molecule, *viz*, 2′-aminothiazolo-[5′,4′:16,17]steroids (class A), 2′-aminothiazolo[5′,4′:20,21]-steroids (class B), 2′-aminothiazolo[5′,4′:2,3]steroids (class C).

Class A.

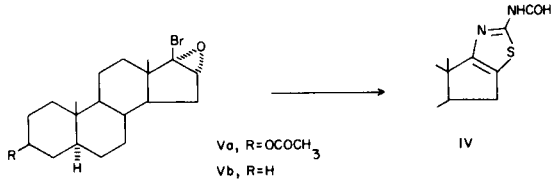
The reaction of 16-bromo-17-ketosteroids with thiourea in dimethylformamide in a 1:2 ratio at reflux temperature for 2-2.5 hours, yielded compounds IVa-IVe. The products were purified by silica gel column chromatography using chloroform as eluent. The compounds prepared in this manner along with their respective yields are shown in Table I. These products were identical with those obtained upon heating 17β-bromo-16α,17α-oxidoandrostan-3β-ol acetate (Va), 17β-bromo-16α,17α-oxidoandrostan (Vb) and thiourea together in *N,N*-dimethylformamide.



III IV

IIIa, R = 3β, CH_3COO, R_1 = 5α
IIIb, R = 3β, CH_3COO, R_1 = 5β
IIIc, R = 3α, CH_3COO, R_1 = 5α
IIId, R = 3, H, R_1 = 5α
IIIe, R = 3β, CH_3COO, R_1 = Δ^5

A plausible pathway for the conversion of V to IV is a concerted process involving ring opening of the epoxide by thiourea at C-16, with the expulsion of bromide and the formation of an acyclic intermediate. It is known that conversion of the halo-epoxides (V) with amines to 16β-amino-17-ketosteroids occurs with ring opening of the epoxide at C-16 (14).



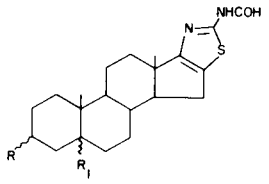
Va, R=$OCOCH_3$
Vb, R=H

IV

Furthermore, 3-acetoxy-16α-bromoestra-1,3,5(10)-trien-17-one (VI) is converted by heating with thiourea in

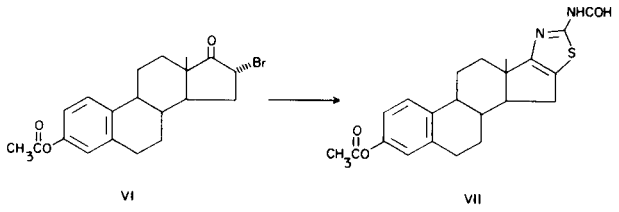
0022-152X/79/040763-06$02.25

Table I



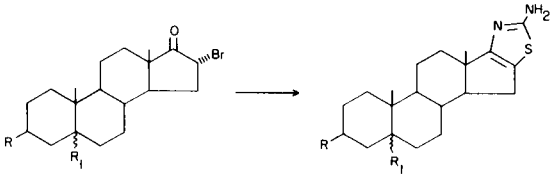
Compound No.	R	R_1	M.p.° C	Formula	Yield %	Calcd. %			Found %		
						C	H	N	C	H	N
IVa	3β, CH_3COO	5α-H	263-264	$C_{23}H_{32}N_2O_3S$	75	66.34	7.69	6.76	66.21	7.77	6.73
IVb	3β, CH_3COO	5β-H	201-202	$C_{23}H_{32}N_2O_3S \cdot 0.5H_2O$	60	64.94	7.76	6.11	64.41	7.32	6.38
IVc	3α, CH_3COO	5α-H	251-253	$C_{23}H_{32}N_2O_3S$	45	66.34	7.69	6.73	66.36	7.51	6.32
IVd	3, H	5α-H	251-252	$C_{21}H_{30}N_2OS$	50	70.26	8.40	7.82	69.89	8.14	7.35
IVe	3β, CH_3COO	Δ^5	278-280	$C_{23}H_{30}N_2O_3OS$	50	66.66	7.24	6.76	66.40	7.51	6.61

dimethylformamide at steam bath temperature to 3-acetoxy-2′-formamidothiazolo[5′,4′:16,17]estra-1,3,5(10),16-tetraen.



VI VII

When the 16α-bromo-17-ketones VIIIa, VIIIb and VIIIc were heated with thiourea in isopropanol, we obtained the 2′-aminothiazolo[5′,4′:16,17]steroids IXa, IXb and IXc, respectively.

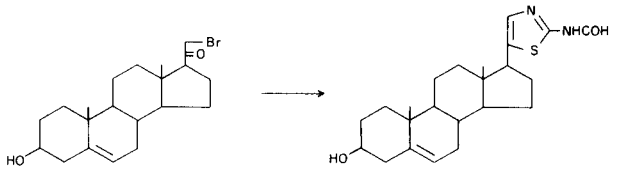


VIIIa, R=H, R_1=5α-H
VIIIb, R=OH, R_1=5α-H
VIIIc, R=$OCOCH_3$, $R_1=\Delta^5$

IXa, R=H, R_1=5α-H
IXb, R=OH, R_1=5α-H
IXc, R=$OCOCH_3$, $R_1=\Delta^5$

Class B.

Extension of this last reaction to 21-bromo-3β-hydroxy-5-pregnen-20-one (X) with thiourea in refluxing dimethylformamide yielded 2′-formamidothiazolo[5′,4′:20,21]-pregna-5,20-dien-3β-ol (XI).



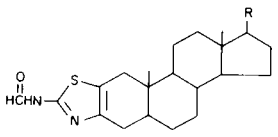
X XI

Class C.

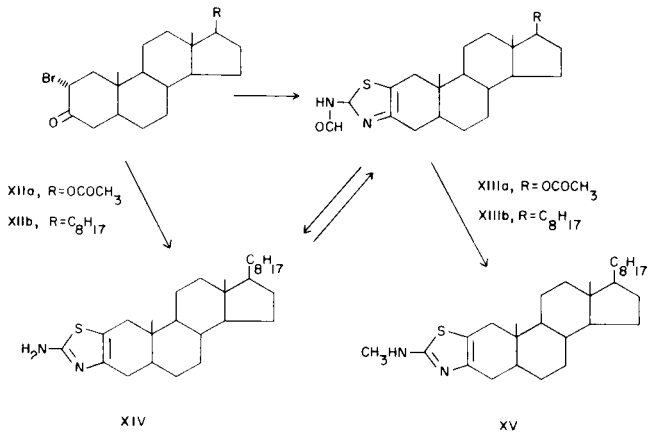
2α-Bromo-3-ketones XIIa and XIIb reacted readily with thiourea in dimethylformamide to give the corresponding 2′-formamidothiazolo[5′,4′:2,3]steroids XIIIa and XIIIb. The compounds prepared in this manner and their respective yields are reported in Table II.

When 2′-formamidothiazolo[5′,4′:2,3]-5α-cholest-2-ene (XIIIb) was treated with dilute sulfuric acid or alcoholic potassium hydroxide, 2′-aminothiazole (XIV) was obtained. Reacting 2α-bromocholestan-3-one with thiourea in

Table II



Compound No.	R	M.p.° C	Formula	Yield %	Calcd. %			Found %		
					C	H	N	C	H	N
XIIIa	CH_3COO	288-290	$C_{23}H_{32}N_2O_3S$	37	66.34	7.69	6.73	66.15	7.86	6.75
XIIIb	C_8H_{17}	250-252	$C_{29}H_{46}N_2OS$	95	74.04	9.78	5.95	73.75	9.62	5.71



2-propanol at reflux temperature gave compound XIV. Treatment of 2′-aminothiazolo[5′,4′:2,3]-5α-colest-2-ene with dimethylformamide at reflux temperature or formyl acetic anhydride at room temperature produced compound XIIIb. The product of lithium aluminum hydride reduction of XIIIb was the 2′-methylaminothiazole (XV). Similar reduction was effected to compound IVe. The singlet for the methyl protons of the 2′-methylamino group appeared in the nmr spectrum of XV and XVI at τ 2.90 and 2.98, respectively.

2′-Aminothiazolo[5′,4′:2,3]-5α-cholest-2-ene (XIV) and 2′-aminothiazolo[5′,4′:16,17]-androsta-5,16-dien-3β-ol acetate (IXc) were tested for antimicrobial activity. Compound XIV had no antimicrobial activity against any of the organisms which were tested, while IXc showed moderate activity. The microorganisms used and the doses for testing are reported in Table III.

Table III

Organism	Compound (a) XIV	IXc
Escherichia coli	NI	NI
Pseudomonas aeruginosa	NI	NI
Streptococcus agalactiae	NI	250
Streptococcus mutans	NI	62.5
Staphylococcus aureus	NI	NI
Corynebacterium sp.	1000	62.5
Norcardia asteroides	NI	125
Candida albicans	NI	250
Saccharomyces cerevisiae	NI	62.5

(a) NI indicates not inhibitory at 1000 μg./ml.; dilutions tested (μg./ml.): 1000, 500, 250, 125, 62.5, 31.25, 15.625, 7,8125.

Infrared Spectra of Aminothiazolosteroids.

The compounds listed in Tables I and II exhibit common features which can easily be correlated. The frequencies of the principal absorption bands of the 2′-aminothiazolosteroids and 2′-formamidothiazolosteroids between 700-3500 cm^{-1} are presented in the following discussion.

The bands in 700-800 cm^{-1} region are probably associated with an out-of-plane bending vibration of the C-H group of the thiazole ring (15). In the case of thiazolosteroids this vibration does not exist except in 2′-formamidothiazolo[5′,4′:20,21]pregna-5,20-dien-3β-ol (XI), which exhibit absorption for the out-of-plane C-H group at 735 cm^{-1}.

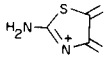
A fairly strong band in the range 840-850 cm^{-1} is found in all 2′-formamidothiazolosteroids and is probably due to the formamido group. This band does not appear in 2′-aminothiazolosteroids, in simple steroids or in α-bromoketo steroids.

It was noticed that the frequency of the 2′-aminothiazole ring appears as a strong band at 1500-1525 cm^{-1}, and that of 2′-formamidothiazole ring at 1520-1550 cm^{-1}. The strong band at 1620-1630 cm^{-1} corresponds to symmetric NH_2 stretching of the 2′-aminothiazolosteroids and in simple molecules of aminothiazole (16). The amides IV, XI and XIII show a strong absorption band near 1670 cm^{-1}.

Primary amines can be identified by the presence of two absorption bands in the NH stretching region between 3500 and 3150 cm^{-1}, arising from the symmetric and asymmetric vibrations of the hydrogen atoms. Often a third peak appears in this region due to hydrogen bonding effects. The absorption bands (NH_2) of the 2′-aminothiazolosteroids appear the following regions: 3420, 3280,3100 cm^{-1} (IXa); 3400, 3260, 3080 cm^{-1} (IXb); 3420, 3280, 3100 cm^{-1} (IXc); and 3430, 3280, 3100 cm^{-1} (XIV).

The frequencies of the principal absorption bands of the -NHCOH group between 3500-3000 cm^{-1} are: 3160, 3030 cm^{-1} (IVa); 3170, 3010 cm^{-1} (IVb); 3310 cm^{-1}; 3150, 3030 cm^{-1} (IVd); 3160, 3020 cm^{-1} (IVe); 3160, 3040 cm^{-1} (XIIIa); and 3430, 3285 cm^{-1} (XIIIb).

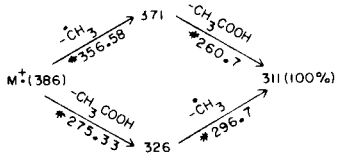
Mass Spectra of Aminothiazolosteroids.

The base peak (100%) of compound XIIIb occured at m/e 126 corresponding to the ion  . A metastable peak at m/e 35.92 shows that this peak (m/e 126) arises directly from M^+, path b. The molecular ion m/e 442, has a medium intensity . Further fragmentation of compound XIIIb is shown in Scheme 1.

The spectrum of IXb reveals a peak (100%) at m/e 331, which originates by the loss of $\dot{C}H_3$ from M^+, as it is shown from m^* at m/e 316.65. The molecular ion at m/e 346 is

rather abundant (50% based on the base peak). The most interesting fragmentation peaks are shown in Scheme 2.

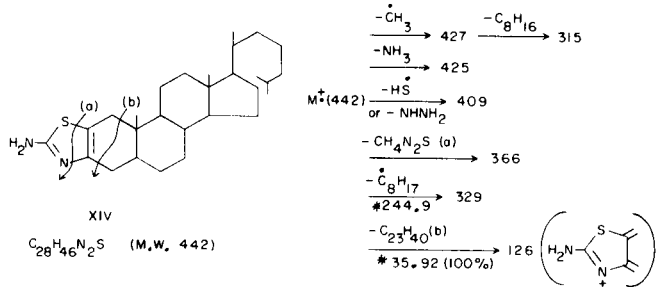
The possible pathways for the formation of the base peak (100%) at m/e 311 of compound IXc are shown below.



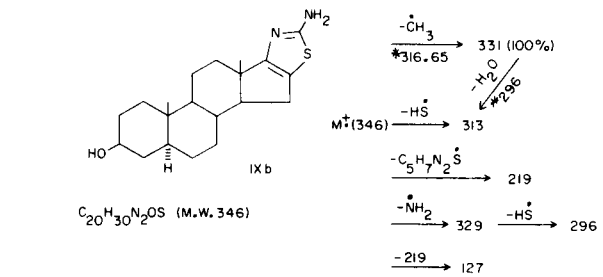
Further, the ion ($M^{\cdot}$ -60) 326 possible arises from $M^{\cdot}$ by the loss of $S=\dot{C}=NH_2$, m/e 60, path b (Scheme 3). Further fragmentation peaks are shown in Scheme 3.

The peaks of the fragmentation of the formamido-thiazolosteroids IVb, IVc, IVd and XI are presented in Schemes 4-7.

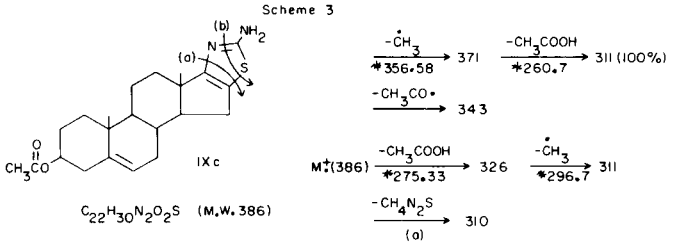
Scheme 1



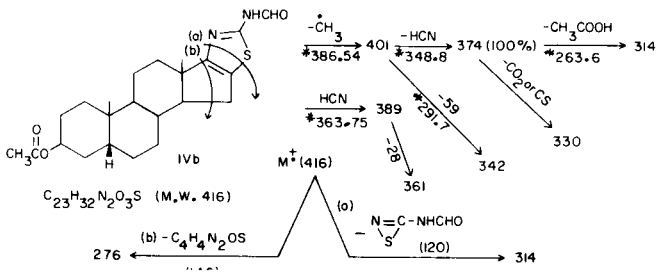
Scheme 2



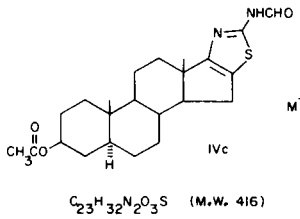
Scheme 3



Scheme 4

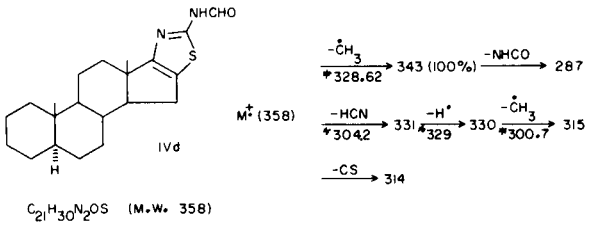


Scheme 5

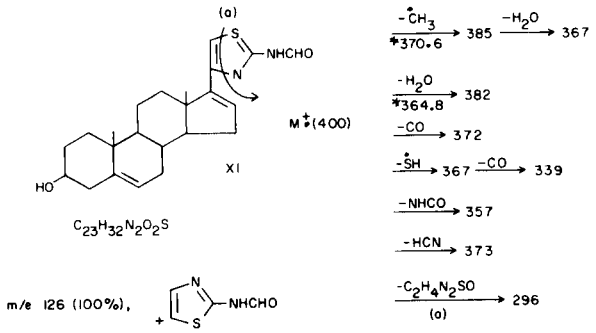


The fragmentation of this compound is similar to that of IVb except for the observed peak intensities. The base peak (100%) is at m/e 401 (M^{+} - $\dot{C}H_3$).

Scheme 6



Scheme 7



Ultraviolet Spectra of Aminothiazolosteroids.

The ultraviolet spectra of the steroid aminothiazole derivatives are listed in Table IV.

Table IV

Compound No.	Solvent	λ Max mμ	Log ε
IVa	Chloroform	287	4.01
IVb	Chloroform	288	3.63
IVc	Ethanol	287	4.13
IVd	Chloroform	291	3.95
IVe	Chloroform	285	4.02
VII	Chloroform	285	3.63
IXa	Chloroform	269	3.92
IXb	Chloroform	271	3.77
IXc	Chloroform	270	3.67
XI	Chloroform	273	3.82
XIIIa	Ethanol	280	4.10
XIIIb	Chloroform	285	3.94
XIV	Ethanol	262	3.96
XV	Chloroform	266	3.63
XVI	Chloroform	273	3.82

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Ir spectra were recorded with a Perkin-Elmer 521 spectrometer in solid phase potassium bromide. Nmr spectra were determined with a Varian Associates A-60 instrument, using deuteriochloroform as a solvent and tetramethylsilane as the internal standard. Thin-layer chromatography was performed on silica gel plates using chloroform-methanol (95:5) as developer. Mass spectra were obtained at 70 eV direct insertion into the ion source of a Hitachi Perkin-Elmer RMU-6M instrument. Ultraviolet spectra are measured in ethanol or chloroform on a Cary Model 17 or on a Techtron 635. Elemental analyses were performed by the Analytical Laboratory of the Chemistry Department, N.R.C., "Demokritos".

Procedures for the Preparation of 2′-Formamidothiazolosteroids (IV, XIII).

A. From α-Bromoketosteroids (III, XII).

To a solution of 20 ml. of *N,N*-dimethylformamide containing 3 mmoles of the bromoketone (17,18), was added 6 mmoles of thiourea and the mixture was heated under reflux for 2 hours. The solution was poured into a saturated solution of sodium carbonate and extracted several times with chloroform. The organic layer was washed with water and dried over sodium sulphate. After evaporation of the solvent the residue was purified by filtration over a column of silica gel (eluent chloroform-methanol, 95:5). After removal of the solvent the residue was cyrstallized from chloroform-methanol. The compounds prepared are reported in Tables I and II.

2′-Formamidothiazolo[5′,4′:20,21]pregna-5,20-dien-3β-ol (XI).

This compound was prepared as described before, using 21-bromo-3β-hydroxy-5-pregnen-20-one (X) (19) and thiourea. The product was purified by silica gel column chromatography (eluent chloroform-methanol 95:5), and crystallized from chloroform-methanol to give XI in 40% yield, m.p. 226-227°.

Anal. Calcd. for $C_{23}H_{32}N_2O_2S$: C, 69.00; H, 8.00; N, 7.00. Found: C, 68.89; H, 8.05; N, 6.95.

B. From 17β-Bromo-16α,17α-oxidoandrostan (V).

A solution of 1 mmole of 17β-bromo-16α,17α-oxidoandrostan (V) (14) and 2 mmoles of thiourea was refluxed with 10 ml. of *N,N*-dimethylformamide for 2 hours. The solution was poured into ice-water; it was neutralized with sodium carbonate and the precipitate was collected by filtration to yield 2-formamidothiazoles IVa and IVd.

2′-Formamidothiazolo[5′,4′:16,17]-5α-androsten-16-3β-ol Acetate (IVa).

This compound had m.p. 263° and an infrared spectrum identical to the compound prepared from 3β-acetoxy-16α-bromo-5α-androstan-17-one and thiourea.

2′-Formamidothiazolo[5′,4′:16,17]-5α-androsten-16 (IVd).

This compound had m.p. 253° and an infrared spectrum identical to the compound prepared from 16α-bromo-5α-androstan-17-one and thiourea.

2′-Aminothiazolo[5′,4′:16,17]-5α-androsten-16-3β-ol (IXb).

To a flask containing 0.830 g. of 16α-bromo-5α-androstan-17-one-3β-ol, 0.265 g. of thiourea, was added 30 ml. of 2-propanol and the mixture was heated under reflux for 24 hours. After this time, cold water was added and the precipitate was collected by filtration. This solid was dissolved in 25 ml. of methanol containing 0.5 g. of potassium hydroxide and the mixture was refluxed for 2 hours. After this time the solution was poured into ice-water and the precipitate was filtered to yield IXb, 0.350 g. Crystallization from methanol-chloroform gave m.p. 292-295°.

Anal. Calcd. for $C_{20}H_{30}N_2OS$: C, 69.36; H, 8.67; N, 8.09. Found: C, 69.67; H, 9.04; N, 7.97.

2′-Aminothiazolo[5′,4′:16,17]androsten-16 (IXa).

This compound was prepared according to the method for the preparation of IXb, in 50% yield after recrystallization from chloroform-methanol m.p. 283-285° dec.

Anal. Calcd. for $C_{20}H_{30}N_2S$: C, 72.72; H, 9.09; N, 8.14. Found: C, 72.14; H, 9.60; N, 8.14.

2′-Aminothiazolo[5′,4′:16,17]androsta-5,16-dien-3β-ol Acetate (IXc).

This compound was prepared according to the method for the preparation of IXb, except that the neutraliztion was effected with sodium carbonate at room temperature. The compound was isolated in pure form after silica gel column chromatography, m.p. 266-268°.

When 150 mg. of IXc was heated under reflux with 20 ml. of *N,N*-dimethylformamide for 20 hours, 2′-formamidothiazolo-[5′,4′:16,17]androsta-5,16-dien-3β-ol acetate (IVe) was obtained, which was identical by melting point and infrared spectrum with the reaction product of 16α-bromoketone, thiourea and *N,N*-dimethylformamide.

2′-Aminothiazolo[5′,4′:2,3]-2-cholesten (XIV).

To a solution of 2α-bromocholestan-3-one (1.713 g., 3 mmoles) in 30 ml. of isopropanol, was added 0.456 g., (6 mmoles) of thiourea and the mixture was heated under reflux for 2 hours. After this time the reaction mixture was poured into a solution of sodium carbonate and the precipitate which formed was filtered to give 1.8 g. of crude aminothiazole. Crystallization from chloroform-methanol gave 1.350 g. of pure XIV, m.p. 255-256° dec.

Anal. Calcd. for $C_{28}H_{46}N_2S$: C, 76.02; H, 10.40; N, 6.33. Found: C, 76.00; H, 10.65; N, 6.15.

2′-Aminothiazolo[5′,4′:2,3]-2-cholesten Hydrobromide.

Two grams of bromocholestanone and 0.532 g. of thiourea was heated on a steam bath with 35 ml. of *N,N*-dimethylformamide for 5 hours. Then the mixture was poured into ice-water and the precipitate was collected by filtration. Crystallization from chloroform-methanol afforded 1.42 g. of the hydrobromide salt of 2′-aminothaizolo[5′,4′:2,3]-2-cholesten, m.p. > 300°.

Anal. Calcd. for $C_{29}H_{47}ClN_2S$: C, 64.24; H, 9.20; N, 5.35. Found: C, 64.29; H, 9.48; N, 5.35.

Hydrolyses of XIIIb with Potassium Hydroxide.

To a solution of 100 mg. of XIIIb in 5 ml. of propanol, was added 3 ml. of a 20% solution of potassium hydroxide and the mixture was allowed to stand at room temperature for 4 days. After this time the solution was poured into water and the precipitate was filtered. Crystallization from methanol-chloroform afforded XIV identical by melting point and infrared spectrum to the compound which was prepared from bromocholestanone and thiourea in 2-propanol.

Hydrolysis of XIIIb with Sulfuric Acid.

A mixture of XIIIb (0.3 g.) and 5 ml. of 50% sulfuric acid was heated under reflux for 2.5 hours. The mixture was poured into water and extracted with chloroform. The solution was washed with water. After drying the organic layer with magnesium sulfate and removal of the solvent under reduced pressure, the residue was crystallized from chloroform-methanol to give XIV.

Formylation of XIV.

A.

A mixture of XIV (0.152 g.) and 10 ml. of *N,N*-dimethylformamide was heated under reflux for 3.5 hours. The reaction mixture was poured into water and the precipitate filtered (0.160 g.) to yield 2′-formamidothiazolo[5′,4′:2,3]-2-cholesten, identical by infrared spectrum and melting point to XIIIb.

B.

A mixture of 5.1 ml. of acetic anhydride and 2.1 ml. of 98% of formic acid was heated at 50-60° for 2 hours. The solution was cooled to room temperature and to this was added 0.4 g. of XIV. The mixture was allowed to stay at room temperature overnight. Then it was poured into ice-water and the precipitate was collected by filtration. This compound was identical by infrared spectrum and melting point to XIIIb.

2'-Methylaminothiazolo[5',4':2,3]-5α-cholest-2-en (XV).

To a solution of 2'-formamidothiazolo[5',4':2,3]-2-cholesten (XIIIb) (1.1 g.) in 100 ml. of anhydrous dioxane, was added lithium aluminum hydride (2 g.) in portions over a period of 15 minutes. After the addition was completed, the reaction mixture was kept under reflux for 20 hours. Excess lithium aluminum hydride was destroyed with ethyl acetate followed by water. The flocculent precipitate was separated by filtration and washed several times with chloroform. The combined filtrates were washed twice with water, dried over magnesium sulfate, and evaporated to yield a residue, which after silica gel column chromatography (eluent chloroform), yielded 0.730 g. of pure compound XV, m.p. 232-233° (chloroform-methanol); ir: ν max 3150 cm^{-1} (NH).

Anal. Calcd. for $C_{29}H_{48}N_2S$: C, 76.31; H, 10.52; N, 6.05. Found: C, 76.52; H, 10.45; N, 6.11.

2'-Methylaminothiazolo[5',4':16,17]androsta-5,16-dien-3β-ol (XVI).

By the procedure described for the reduction of XV, 0.845 g. of 2'-formamidothiazolo[5',4':16,17]androsta-5,16-dien-3β-ol acetate (IVe) was reduced with lithium aluminum hydride (2 g.) in anhydrous dioxane (60 ml.) to give compound XVI, m.p. 237-240 (chloroform-ethanol); ir: ν max: 3320 cm^{-1} (NH).

Anal. Calcd. for $C_{21}N_{30}N_2OS$: C, 70.39; H, 8.37; N, 7.81. Found: C, 70.75; H, 8.27 N, 7.64.

3-Acetoxy-2'-formamidothiazolo[5',4':16,17]estra-1,3,5(10),16-tetraen (VII).

To a solution of 585 mg. of the bromoketone VI (20) in 15 ml. of dimethylformamide, was added 228 g. of thiourea. The mixture was heated on the steam bath for 3.5 hours. The solution was poured into a solution of sodium bicarbonate and the precipitate was collected by filtration. The dry solid was dissolved in chloroform and purified by silica gel column chromatography. Elution with chloroform gave 240 mg. of the aminothiazole VII, m.p. 263° (chloroform-methanol).

Anal. Calcd. for $C_{22}H_{24}N_2O_3S$: C, 66.66; H, 6.06; N, 7.07. Found: C, 66.92; H, 6.24; N, 6.97.

REFERENCES AND NOTES

(1) A. Hantzsch and V. Trauman, *Ann. Chem.*, **249**, 31 (1888).
(2) T. Yoneno, U. S. Patent 3,119,816 (1964).
(3) R. O. Clinton, U. S. Patent 3,081,228 (1963).
(4) K. Takamura and S. Takama, Japanese Patent 22,578 (63) (1961).
(5) K. Takamura and S. Takama, Japanese Patent 22,282 (63) (1961).
(6) K. Takamura and S. Takahisa, Japanese Patent 18,690 (63) (1960).
(7) R. M. Dodson, U. S. Patent 2,705,232 (1955).
(8) J. W. Ralls and C. G. Bergstrom, U. S. Patent 2,793,207 (1957).
(9) T. Yoneno, Japanese Patent 12,924 (63) (1959).
(10) Roussell-UCLAF, Netherlands Appl. 6,610,322 (1966).
(11) P. Catsoulacos, *J. Heterocyclic Chem.*, **10**, 93 (1974); P. Catsoulacos and E. Souli, *ibid.*, **11**, 87 (1975); P. Catsoulacos and E. Souli, *ibid.*, **11**, 193 (1975); P. Catsoulacos and N. Kyriakidis, *ibid.*, **11**, 757 (1975); P. Catsoulacos and N. Kyriakidis, *ibid.*, **11**, 1313 (1975); P. Catsoulacos and E. Souli, *Bull. Soc. Chim.* France, 1313 (1975).
(12) K. Takeda and T. Kameno, *Chem. Pharm. Bull.*, **10**, 1113 (1962).
(13) T. Yomeno, U. S. Patent 3,119,816 (1964).
(14) A. Hassner and P. Catsoulacos, *J. Org. Chem.*, **32**, 549 (1967).
(15) A. Taurins, J.G.E. Fenyes and N. Jones, *Can. J. Chem.*, **35**, 423 (1957).
(16) J. Chouteau, D. Davidovics, J. Metzger and A. Bonzom, *Spectrochim. Acta*, **22**, 719 (1966).
(17) E. R. Glazier, *J. Org. Chem.*, **27**, 2937 (1962).
(18) E. R. Glazier, *ibid.*, **27**, 4396 (1962).
(19) J. F. W. Keana and R. R. Schumaker, *Tetrahedron*, **26**, 5191 (1970).
(20) J. Pataki and G. Siade, *J. Org. Chem.*, **37**, 2127 (1972).