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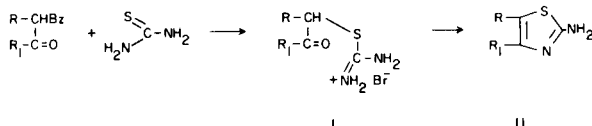
The treatment of 16 α -bromo-17-ketosteroids and 2-bromo-3-ketosteroids with thiourea in dimethylformamide give the corresponding 2'-formamidothiazolosteroids.

The resulting 2'-formamidothiazoles were identical with those obtained in a similar reaction from 17 β -bromo-16 α ,17 α -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.

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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 -halo-carbonyl 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).



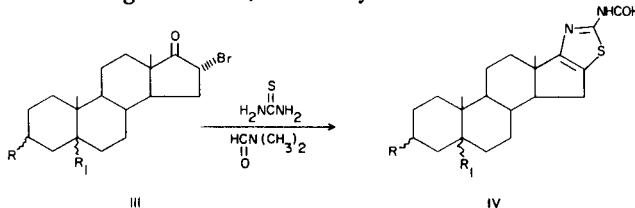
Aminothiazole derivatives of steroids are well known as useful antagonists to hormonal substances (2), as agents which lower the blood pressure of mammals (3), as cardiotonic and hypertensive agents (4-6), which regulate the cardiovascular system (7), for their digitalis regulating effect on cardiac 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 0022-152X/79/040763-06\$02.25

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 17 β -bromo-16 α ,17 α -oxidoandrostane-3 β -ol acetate (Va), 17 β -bromo-16 α ,17 α -oxidoandrostane (Vb) and thiourea together in *N,N*-dimethylformamide.



IIIa, R = 3 β , CH₃COO, R₁ = 5 α

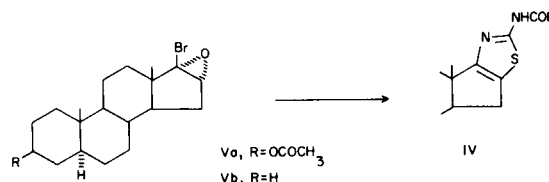
IIIb, R = 3 β , CH₃COO, R₁ = 5 β

IIIc, R = 3 α , CH₃COO, R₁ = 5 α

IIId, R = 3, H, R₁ = 5 α

IIIe, R = 3 β , CH₃COO, R₁ = 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 16 β -amino-17-ketosteroids occurs with ring opening of the epoxide at C-16 (14).



Va, R = OCOCH₃

Vb, R = H

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

Compound No.	R	M.p. ° C	Formula	Yield %	Calcd. %			Found %		
					C	H	N	C	H	N
XIIIa	CH ₃ COO	288-290	C ₂₃ H ₃₂ N ₂ O ₃ S	37	66.34	7.69	6.73	66.15	7.86	6.75
XIIIb	C ₆ H ₁₇	250-252	C ₂₉ H ₄₄ N ₂ OS	95	74.04	9.78	5.95	73.75	9.62	5.71

The spectrum of IXb reveals a peak (100%) at m/e 331, which originates by the loss of $\dot{\text{C}}\text{H}_3$ from M^+ , as it is shown from m^+ at m/e 316.65. The molecular ion at m/e 346 is

Compound No.	Solvent	λ Max $m\mu$	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 crystallized from chloroform-methanol. The compounds prepared are reported in Tables I and II.

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

This compound was prepared as described before, using 21-bromo-3 β -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 $C_{22}H_{32}N_2O_2S$: C, 69.00; H, 8.00; N, 7.00. Found: C, 68.89; H, 8.05; N, 6.95.

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

A solution of 1 mmole of 17 β -bromo-16 α ,17 α -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]-5 α -androsten-16-3 β -ol Acetate (IVa).

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

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

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

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

To a flask containing 0.830 g. of 16 α -bromo-5 α -androstan-17-one-3 β -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-3 β -ol Acetate (IXc).

This compound was prepared according to the method for the preparation of IXb, except that the neutralization 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-3 β -ol acetate (IVe) was obtained, which was identical by melting point and infrared spectrum with the reaction product of 16 α -bromoketone, thiourea and *N,N*-dimethylformamide.

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

To a solution of 2 α -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'-aminothiazolo[5',4':2,3]-2-cholesten, m.p. > 300°.

Anal. Calcd. for $C_{28}H_{47}ClN_2S$: 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]-5 α -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 $\text{C}_{29}\text{H}_{48}\text{N}_2\text{S}$: 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-3 β -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-3 β -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 $\text{C}_{31}\text{H}_{50}\text{N}_2\text{OS}$: 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 $\text{C}_{23}\text{H}_{34}\text{N}_2\text{O}_3\text{S}$: C, 66.66; H, 6.06; N, 7.07. Found: C, 66.92; H, 6.24; N, 6.97.

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