in 1% acetone–Ringer buffer (10 μg/ml) were left for appropriate periods at 37° under light protection in the absence of enzyme. The enzyme inhibitory potency of the aged solutions was assayed by adding glucose-6-phosphate dehydrogenase for an additional incubation period of 5 min.

The results shown in Fig. 3 indicate that the gradual disappearance of anthralin during the first 30 min was responsible for the concomitant decrease in the enzyme inhibitory potency of the solution. The reappearance of a stronger inhibitory activity, however, is in striking contrast with the complete degradation of anthralin which occurred during the following 2–3 hr and, as already noted, could not be attributed to the formation of the dimer.

Similarly, when anthralin was left in acetone (0.5 mg/ml) for several days under continuous exposure to light (Fig. 1), the final dark brown solution, which was totally devoid of anthralin or dimer, showed a strong toxicity against glucose-6-phosphate dehydrogenase (Fig. 1A). Incubation of 1% of the acetone solution with the enzyme in Ringer buffer (5 min) resulted in a total destruction of enzymatic activity, which could not be explained by the presence of quinone.

CONCLUSION

Using a highly sensitive and reproducible HPLC assay, additional evidence has been given for the chemical instability of anthralin in solution, particularly aqueous media. In acetone solution over long periods, anthralin decomposes, in part *via* the dimer, to give a final solution containing 20% quinone. In aqueous media at pH 7.5, 37°, and under light protection, the corresponding dimer (but not quinone) is formed. Near their upper limit of solubility in Ringer buffer, anthralin, dimer, and quinone interact with glucose-6-phosphate dehydrogenase, but this interaction leads to a fairly modest decrease of enzymatic activity. The dramatic changes regarding inhibition of the enzyme cannot be explained by the formation of dimer from anthralin and suggest that other breakdown products, unidentified as yet, must be the most active derivatives against glucose-6-phosphate dehydrogenase. Thus, if neutral aqueous buffers are used for the investigation of the mode of action of anthralin, the chemical instability of this molecule and the possible interference of highly active breakdown products should be kept in mind. Therefore, both *in vitro* and *in vivo* data should be interpreted cautiously.

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Steroidal Oxazoline Derivatives: Synthesis and *In Vitro* Effect on Bovine Pancreatic Ribonuclease Activity

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Abstract □ A series of steroidal oxazoline derivatives, containing different chains attached to the heterocyclic ring, were synthesized and examined for *in vitro* effect on bovine pancreatic ribonuclease activity. The results indicated weak anabolic properties for all products except Compounds III and XII which showed mild catabolic activities.

Keyphrases □ Oxazoline—steroidal derivatives, synthesis and *in vitro* effect on bovine pancreatic ribonuclease activity □ Derivatives—steroidal oxazoline, synthesis and *in vitro* effect on bovine pancreatic ribonuclease activity □ Ribonuclease activity—bovine, pancreatic, steroidal oxazoline derivatives, synthesis and *in vitro* effects

In connection with a program studying modified steroids, a variety of *N,N*-disubstituted aminoethyl ethers of 6-phenyl, benzyl, or thiazolidinyl-17β-estradiol were synthesized and tested for antiestrogenic properties (1). In addition, various androgenic and estrogenic keto-steroids were converted into the corresponding 4-substituted-3-thiosemicarbazone (2) and acylhydrazone (3–5) derivatives, and the products evaluated for anticancer (2, 4) and endocrinological (2, 3, 5) activities.

Extending the studies to steroids containing fused heterocyclic systems, the synthesis of a series of 2′-thio-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazolines (V, VII, IX, and XI) and the corresponding estra-1,5(10)-dieno[4,3-*d*]oxazolines (VI, VIII, X, and XII), possessing methyl or *N,N*-disubstituted aminoethyl moieties in the heterocyclic ring, was undertaken[1]. The *in vitro* effect of the product on the activity of the bovine pancreatic ribonuclease was evaluated as a preliminary measure for their anabolic and catabolic properties (6) (Scheme I).

RESULTS AND DISCUSSION

Chemistry—The 2- (I) and 4-aminoestrones (II), prepared by reduction of the 2- and 4-nitroestrones (7) with sodium dithionite in alkaline medium (8), were treated with carbon disulfide and potassium hydroxide in boiling ethanol to produce 2′-thio-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoline (III), and 2′-thio-17-oxoestra-1,5(10)-dieno[4,3-

[1] This paper constitutes Part VII of the series on Steroidal Derivatives: Part VI is Ref. 5.

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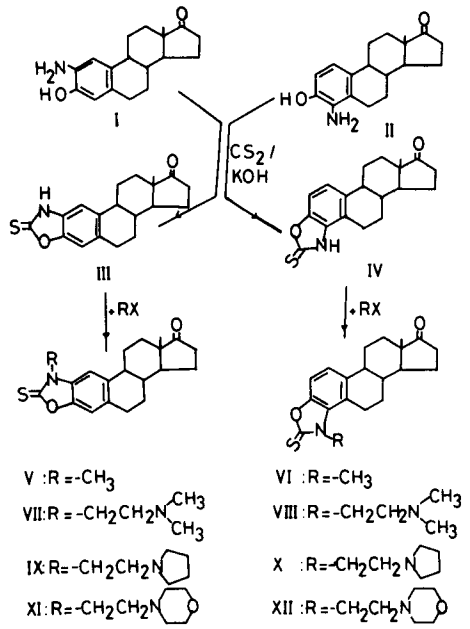
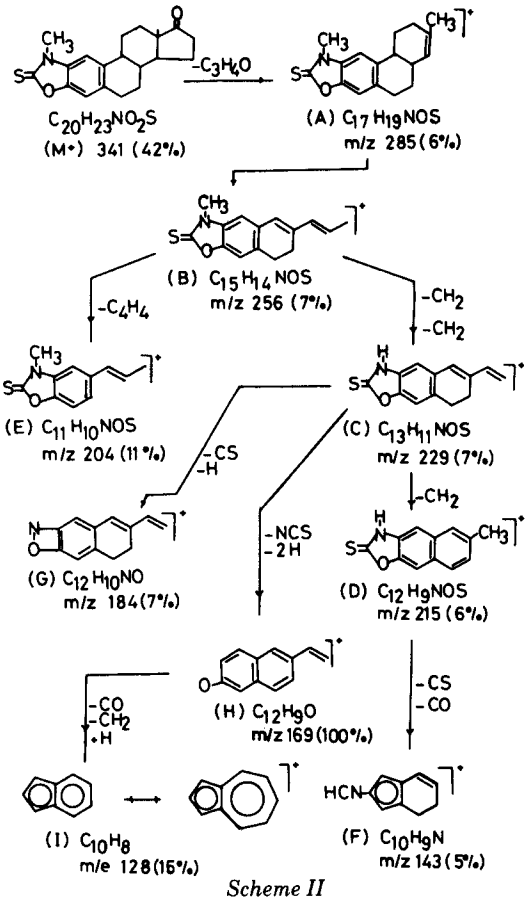


Scheme I

d]oxazoline (IV), respectively. The reaction of Compound III with methyl iodide in cold aqueous sodium hydroxide solution yielded the corresponding *N*-methylsteroidal oxazoline derivative (V). The application of the same procedure to synthesize the other required compounds (VI–XII) was fruitless. The preparation of the 3′-[2-(*N*-pyrrolidinyl)-ethyl] derivative (IX) necessitated the reaction of 2′-thioxazoline (III) with 2-(*N*-pyrrolidinyl)ethyl chloride hydrochloride salt in refluxing sodium ethoxide solution, while for compounds VI–VIII and X–XII, the use of potassium hydroxide in boiling acetone was the most effective in conducting the reaction to completion. The products (Table I) were identified by IR, UV, PMR, and, for one representative example, by mass spectra. The IR spectra of the products lacked the C=N absorption bands and exhibited a band at 930 cm^{-1} for the C=S absorption (9).

In the PMR spectra (Table II), the steroidal[2,3-*d*]oxazolines (V, VII, IX, and XI) showed two singlets at 7.08–7.20 and 7.27–7.59 ppm for the C_4 and C_1 protons of the steroidal skeleton. The analogous steroidal[4,3-*d*]oxazolines (VI, VIII, X, and XII) showed the C_1 and C_2 protons as a singlet at 7.20 ppm. The C_{18}—CH_3 of all products as well as the N—CH_3 of Compounds V and VI resonated as two singlets at 0.91–0.92 and 2.71–2.75 ppm, respectively. The protons of the 2-methylene chain of Compounds VII–XII were identified as two triplets resonating at



Scheme II

different chemical shifts. The first, appearing at 2.21–2.88 ppm, was assigned to the more shielded methylene protons adjacent to the *N*-dimethyl, pyrrolidino, or morpholino function. The other triplet, resonating at 3.42–3.49 ppm, was assigned to the relatively less shielded methylene protons attached to the oxazoline ring. The spectra also showed the signals for the pyrrolidine and morpholine protons at the expected chemical shift in the high field region.

The mass spectrum of Compound V showed a molecular ion peak at *m/z* 341. Its fragmentation as demonstrated in Scheme II involved the cleavage of Ring D to give Ion A at *m/z* 285 which after cleavage of Ring

Table I—Synthesized Steroidal Oxazoline Derivatives (V–XII)

Compound No.	Yield, %	Melting Point	Molecular Formula	Analysis, % Calc.	Found
V	63	204–205[a]	$C_{20}H_{23}NO_2S$	C 70.36	70.27
				H 6.79	6.82
				N 4.10	4.24
VI	87	186–187	$C_{20}H_{23}NO_2S$	C 70.36	70.37
				H 6.79	7.00
				N 4.10	4.26
VII	70	146–147	$C_{23}H_{30}N_2O_2S$	C 69.32	69.14
				H 7.59	7.85
				N 7.03	7.13
VIII	70	144–145	$C_{23}H_{30}N_2O_2S$	C 69.32	69.43
				H 7.59	7.74
				N 7.03	6.90
IX	93	157–158	$C_{25}H_{32}N_2O_2S$	C 70.72	70.54
				H 7.60	7.88
				N 6.60	6.47
X	85	157–158	$C_{25}H_{32}N_2O_2S$	C 70.72	70.37
				H 7.60	7.80
				N 6.60	6.60
XI	82	173–174	$C_{25}H_{32}N_2O_3S$	C 68.16	68.07
				H 7.32	7.29
				N 6.36	6.52
XII	67	179–180	$C_{25}H_{32}N_2O_3S$	C 68.16	67.98
				H 7.32	7.58
				N 6.36	6.54

[a] All products were crystallized from ethanol except compounds VII and X, which were crystallized from aqueous ethanol.

C produced Ion B at *m/z* 256. Successive elimination of methylene groups from Ion B gave Ions C, D, and E at *m/z* 229, 215, and 204, respectively. Ion D then lost a carbon monosulfide and a carbon monoxide function, and produced the isocyanide Ion F at *m/z* 143. Ion C either eliminated carbon monosulfide and a hydrogen to give Ion G at *m/z* 184 or underwent cleavage of an isothiocyanate ion and two hydrogens to yield Ion H as the base peak at *m/z* 169. This in turn eliminated carbon monoxide and a methylene ion and accepted a hydrogen giving Ion I at m/z 128. The spectrum has also shown the various ions reported for the normal fragmentation of estrone (10) and oxazole (11, 12).

Biological Screening—Compounds III–V, VII–IX, XI, and XII were *in vitro* tested for possible anabolic–catabolic activity by measuring their effects on the activity of the bovine pancreatic ribonuclease. The applied method, as reported (6), involved the utilization of four sets of incubation media: the medium containing the steroidal derivative and the enzyme, the blank lacking the enzyme, the control devoid of the steroidal derivative, and the control blank containing the enzyme and the phosphate buffer solution. After mixing the components of each set, the tubes were incubated at 37° for 15 min, and treated with an ethanol–glacial acetic acid mixture to terminate the reaction. They were stored for 1 hr in the refrigerator, centrifuged for 15 min, and the supernates were spectrophotometrically measured at 260 nm. The activity of the ribonuclease was calculated according to a previous report (13) and the data expressed as the mean values of five experiments ± standard deviation in units per milliliter.

In accordance with the results obtained (Table III), the majority of products caused a weak percentage inhibition of ribonuclease indicating mild anabolic properties. Compounds III and XII, induced a weak percentage activation of ribonuclease and hence proved to be of mild catabolic nature. In contrast to such findings, a variety of compounds having a heterocyclic ring fused to the 2,3- or 3,4-positions of various steroids have been reported to possess more potent endocrinological activity than the parent steroidal nuclei (14–19).

EXPERIMENTAL[2]

2′-Thiosteroidal-oxazolines III and IV—A mixture of the aminosterone (I or II) (8) (150 mg, 0.52 mmole), carbon disulfide (3.5 ml), and potassium hydroxide (30 mg) in ethanol (20 ml) was heated under reflux for 6 hr. The final solution was concentrated, cooled to room temperature, acidified with glacial acetic acid, treated with enough water until permanent turbidity, and left overnight in the refrigerator. The deposited white solid was filtered, washed with water, and crystallized from ethanol giving the required products. Compound III was obtained as white shiny scales darkening at 280°, mp 310°, yield: 87%. Compound IV was produced as white prisms, mp 188–192°, yield: 99%. IR (mineral oil): 1730 (C=O), 1510, 1495, 1140, and 930 cm^{-1} (H—N—C=S amide I, II, III, and IV bands, respectively) (9). UV of Compound IV, λ_{max} (ethanol) (log ϵ): 225 (4.477), 265 (4.202), 270 (4.180), 300 (sh) (4.503), and 310 nm (4.982). The products give microanalytical data within ±0.4% for C, H, and N.

2′-Thio-3′-methyl-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoline (V)—Methyl iodide (90 mg, 0.63 mmole) was added dropwise to an ice-cooled solution of 2′-thio-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoline (III) (200 mg, 0.61 mmole) in a mixture of ethanol (10 ml) and 10% aqueous potassium hydroxide solution (10 ml). The mixture was stirred for 1 hr, while being cooled in ice, and for an additional hour at room temperature. The final solution, containing some deposited products, was left overnight in the refrigerator, filtered, and the product crystallized from ethanol to give white shiny scales of the required Compound V. IR (mineral oil): 1720 (C=O) and 920 cm^{-1} (C=S). The yield and physical constants of the product are recorded in Table I. Mass spectrum of V showed *m/z* (relative abundance %) M^+ at 341 (42), 285 (6), 284 (6), 257 (4), 256 (7), 243 (8), 242 (4), 231 (9), 230 (13), 229 (7), 228 (11), 218 (5), 217 (18), 216 (13), 215 (6), 204 (11), 191 (11), 184 (7), 183 (11), 182 (9), 180 (3), 179 (5), 178 (26), 172 (5), 170 (9), 169 (100), 167 (5), 166 (4), 165 (6), 164 (6), 158 (7), 157 (15), 156 (5), 155 (7), 154 (6), 153 (8), 152 (5), 145 (4), 144 (4), 143 (5), 142 (6), 141 (11), 140 (5), 131 (8), 130 (6), 129 (15), 128 (15), 127 (6), 117 (5), 116 (15), 115 (22), 103 (15), 91 (6), 79 (4), 77 (6), 67 (6), 55 (6), and 41 (6).

2′-Thio-3′[2-(*N*-pyrrolidino)ethyl]-17-oxoestra-1(10),4-dieno-[2,3-*d*]oxazoline (IX)—2-(*N*-Pyrrolidinyl)ethyl chloride hydrochloride (110 mg, 0.6 mmole) was added to a solution of the thione derivative III (200 mg, 0.61 mmole) in sodium ethoxide (prepared from 30 mg of sodium metal and 10 ml of absolute ethanol) and the mixture was heated under reflux for 1 hr. The formed inorganic salt was filtered from the hot mixture and the filtrate concentrated to give, after cooling, the required product IX (Table I). IR (mineral oil): 1720 (C=O) and 920 cm^{-1} (C=S).

2′-Thio-3′-substituted-17-oxoestra-1(10),4-dieno[2,3-*d*]-and-1,5(10)-dieno[4,3-*d*]oxazolines (VI–VIII and X–XII)—A mixture of the steroidal 2′- (III) or 4′-thione (IV) derivative (200 mg, 0.61 mmole), potassium hydroxide (70 mg, 1.25 mmoles), and one molar equivalent of the selected alkyl, dialkylaminoalkyl, or *N*-heteroalkyl halide in acetone (15 ml) was heated under reflux for 2.5–12 hr (TLC). Filtration while hot, to remove the inorganic salt, and concentration of the acetone solution followed by treatment with water gave the required products identified as shown in Tables I and II. IR (mineral oil): 1730–1725 (C=O) and 965–920 cm^{-1} (C=S). UV of Compound VIII λ_{max} (ethanol) (log ϵ): 220 (4.449), 258 (4.303), 280 (4.181), and 290 nm (4.142).

Materials and Methods for the *In Vitro* Anabolic–Catabolic Activities—The following four sets of solutions were used in the evaluation procedures:

1. A 0.05 *M* phosphate buffer (pH 7.4);
2. A solution of 5 mg of a highly polymerized yeast RNA in 1 ml of the phosphate buffer;
3. A solution of 2.5 mg of bovine pancreatic ribonuclease[3] in 100 ml of distilled water;
4. Various molar concentrations (10^{-6} to 10^{-9}) of the steroidal derivatives in ethanol.

The media utilized were:

1. The medium containing the steroidal derivative and the enzyme was composed of a mixture of 0.4 ml of RNA solution, 0.4 ml of phosphate buffer, 0.1 ml of the steroidal solution, and 0.1 ml of ribonucleotase.
2. The blanks did not contain the enzyme but were composed of a mixture of 0.4 ml of RNA solution, 0.1 ml of the steroidal solution, and 0.5 ml of the buffer.
3. The control experiments were devoid of the steroidal components and contained a mixture of 0.1 ml of ribonucleotase, 0.4 ml of RNA, and 0.5 ml of the buffer solution.
4. The blank of the control contained only 0.4 ml of RNA completed to 1 ml volume by the buffer solution.

Table II—PMR Spectral Data of the Synthesized Steroidal Oxazoline Derivatives

Compound No.	Chemical Shift (δ ppm) in $CDCl_3$
III	0.92 (s, 3H, C_{18}—CH_3), 7.08 (s, 1H, C_4—H), 7.27 (s, 1H, C_1—H), 10.55 (broad and diffused singlet, disappearing on deuterization, 1H, N—H).
V	0.91 (s, 3H, C_{18}—CH_3), 2.71 (s, 3H, N—CH_3), 7.13 (s, 1H, C_4—H), 7.52 (s, 1H, C_1—H).
VI	0.93 (s, 3H, C_{18}—CH_3), 2.75 (s, 3H, N—CH_3), 7.2 (s, 2H, C_1 and C_2—H).
VII	0.91 (s, 3H, C_{18}—CH_3), 2.30 (s, 6H, $N(CH_3)_2$), 2.73 (t, 2H, J = 7 Hz, CH_2—$N(CH_3)_2$), 3.42 (t, 2H, J = 7 Hz, $CH_2CH_2N(CH_3)_2$), 7.13 (s, 1H, C_4—H), 7.51 (s, 1H, C_1—H).
VIII	0.92 (s, 3H, C_{18}—CH_3), 2.30 (s, 6H, —$N(CH_3)_2$), 2.21 (t, 2H, J = 7 Hz, —CH_2—$N(CH_3)_2$), 3.43 (t, 2H, J = 7 Hz, —$CH_2CH_2N(CH_3)_2$), 7.20 (s, 2H, C_1 and C_2—H).
IX	0.91 (s, 3H, C_{18}—CH_3), 2.9 (t, 2H, J = 7 Hz, CH_2—N), 3.49 (t, 2H, —CH_2CH_2N), 7.2 (s, 1H, C_4—H), 7.59 (s, 1H, C_1—H).
X	0.91 (s, 3H, C_{18}—CH_3), 2.88 (t, 2H, J = 7 Hz, CH_2—N), 3.46 (t, 2H, J = 7 Hz, —CH_2CH_2N), 7.2 (s, 2H, C_1 and C_2—H).
XI	0.91 (s, C_{18}—CH_3), 2.4–2.61 (m, 4H, morpholine protons), 2.77 (t, 2H, J = 7 Hz, —CH_2N), 3.45 (t, 2H, J = 7 Hz, —CH_2CH_2N), 3.62–3.80 (m, 4H, morpholine protons adjacent to oxygen), 7.15 (s, 1H, C_4—H), 7.50 (s, 1H, C_1—H).
XII	0.92 (s, 3H, C_{18}—CH_3), 2.45–2.65 (m, 4H, morpholine protons), 2.78 (t, 2H, J = 7 Hz, —CH_2—N), 3.46 (t, 2H, J = 7 Hz, —CH_2CH_2N), 3.63–3.81 (m, 4H, morpholine protons adjacent to oxygen), 7.20 (s, 2H, C_1 and C_2—H).

[2] All melting points are uncorrected. IR spectra were measured as Nujol mulls on a Beckman 4210 IR spectrophotometer. UV spectra for ethanol solution on a Perkin-Elmer 650 S spectrophotometer. PMR and MS were measured on a Perkin-Elmer R32 and an AEI-MS-50, respectively.

[3] Sigma Chemical Co., St. Louis, Mo.

Table III—*In Vitro* Effects of the Synthesized Steroidal Oxazoline Derivatives on the Activity of Bovine Pancreatic Ribonuclease

Compound No.		Molar Concentration of the Compound (M)			
		10^{-6}	10^{-7}	10^{-8}	10^{-9}
Estrone	Mean ± SE[a]	219.6 ± 10.03	225.4 ± 20.04	231.2 ± 14.4	230 ± 17.02
	% Activation	12.46	15.61	18.57	17.98
	p	>0.05	>0.05	>0.05	>0.05
	Control		(208.6 ± 18.6)		
III	Mean ± SE	235.8 ± 21.8	215.0 ± 12.9	205.8 ± 13.5	205.8 ± 23.5
	% Activation	12.89	3.37	1.45	1.45
	p	>0.05	>0.05	>0.05	>0.05
IV	Mean ± SE	187.28 ± 12.4	186.1 ± 12.7	215.0 ± 12.8	218.5 ± 11.7
	% Inhibition	10.1	10.62	3.36	4.81
	p	>0.05	>0.05	>0.05	>0.05
V	Mean ± SE	172.5 ± 13.2	179.3 ± 19.7	195.7 ± 18.5	198.2 ± 12.6
	% Inhibition	17.15	13.79	5.92	4.81
	p	>0.05	>0.05	>0.05	>0.05
VII	Mean ± SE	183.3 ± 13.3	183.3 ± 16.2	207.4 ± 17.4	205.5 ± 15.6
	% Inhibition	12.02	12.02	0.48	1.45
	p	>0.05	>0.05	>0.05	>0.05
VIII	Mean ± SE	194.4 ± 14.4	186.1 ± 16.6	197.22 ± 13.6	212.9 ± 18.9
	% Inhibition	6.62	10.58	5.29	1.92
	p	>0.05	>0.05	>0.05	>0.05
IX	Mean ± SE	200.9 ± 12.6	204.6 ± 12.9	234.3 ± 16.9	230.5 ± 15.6
	% Inhibition	3.51	1.73	12.5	10.58
	p	>0.05	>0.05	>0.05	>0.05
XI	Mean ± SE	200.8 ± 15.8	199.1 ± 16.3	213.7 ± 13.9	222.5 ± 17.6
	% Inhibition	3.55	4.37	2.74	6.87
	p	>0.05	>0.05	>0.05	>0.05
XII	Mean ± SE	221.3 ± 12.9	249.1 ± 17.4	211.8 ± 13.6	220.3 ± 17.7
	% Activation	6.25	19.71	1.45	5.77
	p	>0.05	>0.05	>0.05	>0.05

[a] The ribonuclease activity is expressed in units as the mean ± SE.

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