Novel 2′-Substituted Amino-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazole and Estra-1,5(10)-dieno[4,3-*d*]oxazole Derivatives: Synthesis and *in vitro* Anabolic-Catabolic Activities (1)

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Two novel series of 2′-substituted aminosteroidal[2,3-*d*]- and [4,3-*d*]oxazole derivatives were synthesized and tested *in vitro* for anabolic-catabolic properties. The products showed almost the same activities possessed by the parent steroidal hormone.

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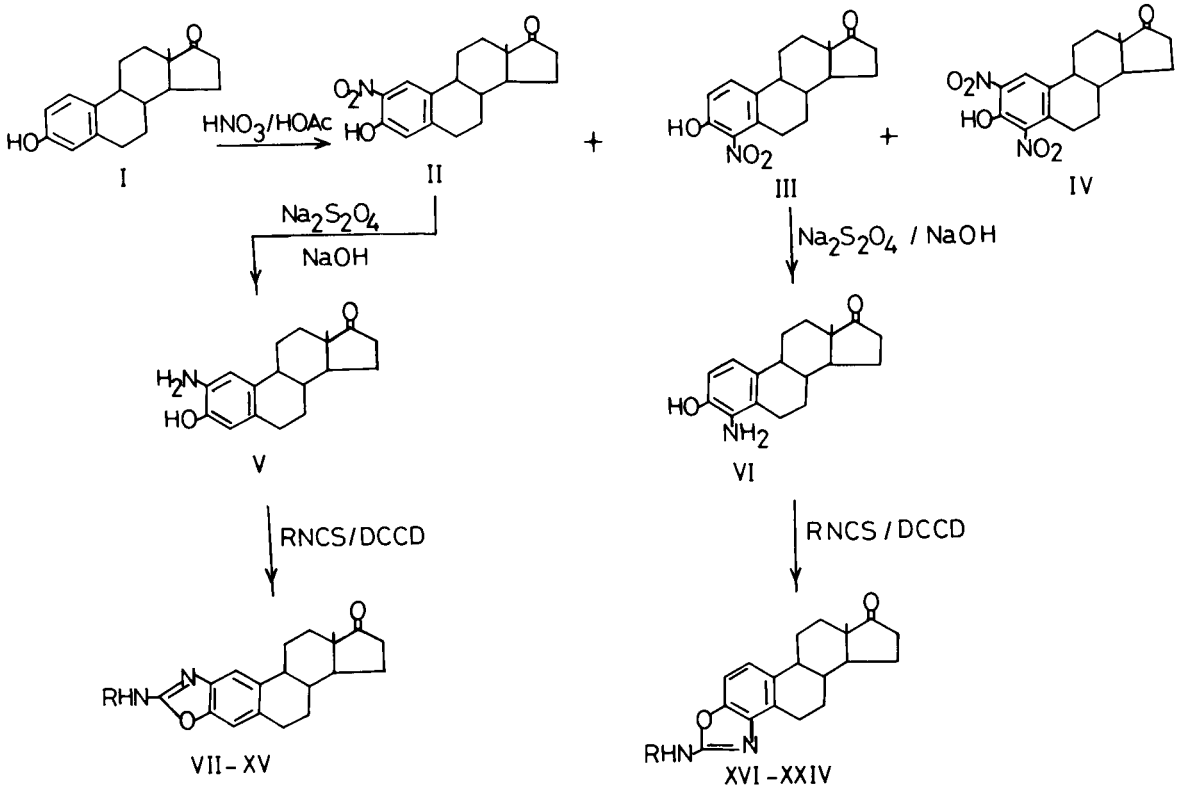
Studies of the biological activities of steroidal heterocycles revealed that the fusion of an isooxazole (2), thiazole (3-6), pyrazole (7,8), oxadiazole (9,10), or a triazole (6,11) ring to the 2,3-positions of various steroids was effective in the production of a variety of compounds possessing anabolic (3,11-14), antiprogestational (2,12), anti-inflammatory (15-17), contraceptive (18) and anticancer (19) properties. In addition, when a thiazoline (20) or a

Scheme I:



VII	:R = C_6H_{11} (c)	XI	:R= $C_6H_4CH_3$(p)
VIII	:R = $CH_2C_6H_5$	XII	:R=$C_6H_4OCH_3$(p)
IX	:R = C_6H_5	XIII	:R= C_6H_4F(p)
X	:R = $C_6H_4CH_3$(m)	XIV	:R= C_6H_4Cl(p)
		XV	:R= C_6H_4Br(p)

XVI	:R=C_6H_{11}(c)	XX	:R=$C_6H_4CH_3$(p)
XVII	:R=$CH_2C_6H_5$	XXI	:R=$C_6H_4OCH_3$(p)
XVIII	:R=C_6H_5	XXII	:R=C_6H_4F(p)
XIX	:R=$C_6H_4CH_3$(p)	XXIII	:R=C_6H_4Cl(p)
		XXIV	:R=C_6H_4Br(p)

Scheme II:

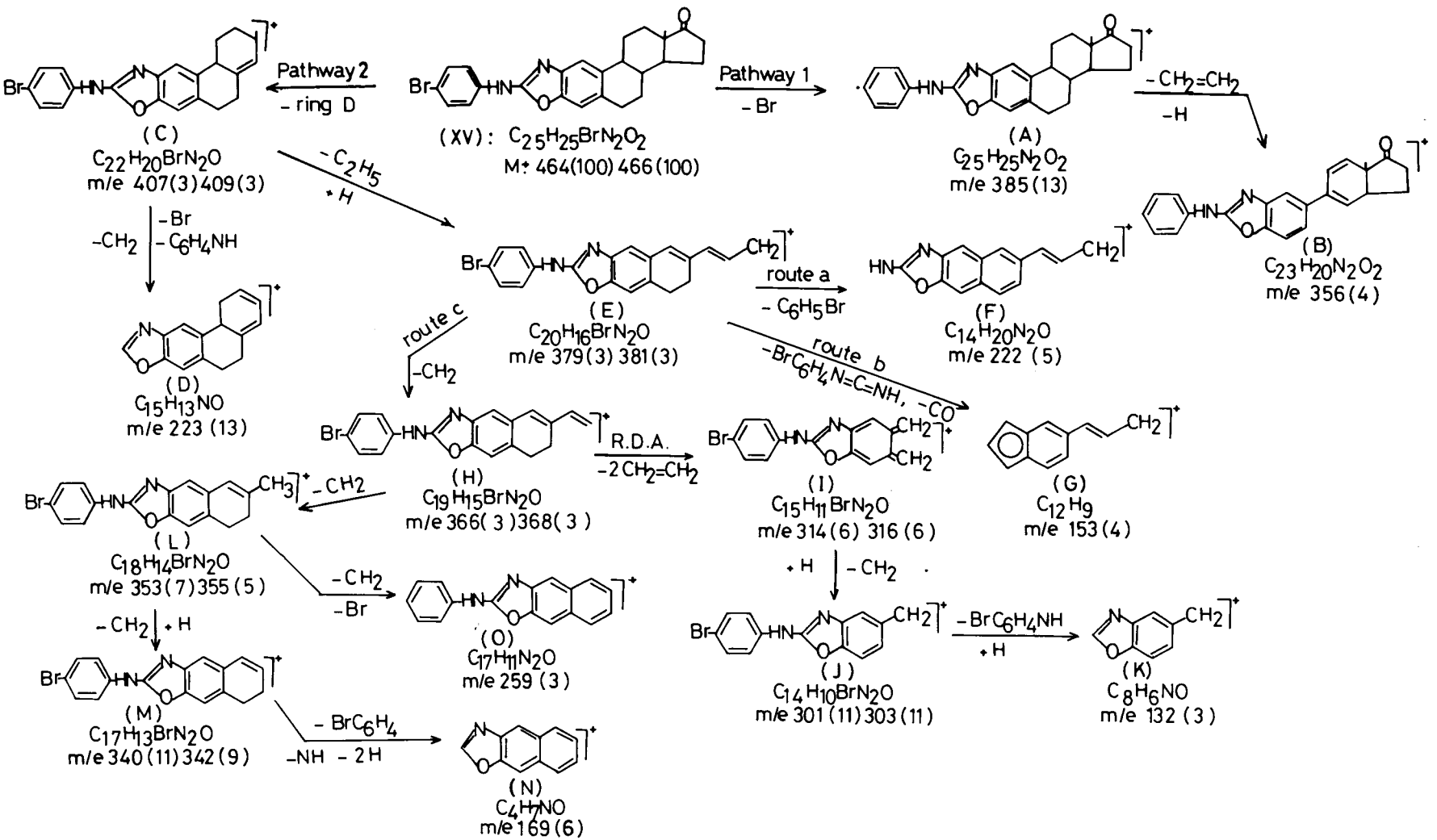

Pathway 2
- ring D
Pathway 1
- Br
- CH2=CH2
-H
(C)
C22H20BrN2O
m/e 407(3) 409(3)
(XV): C25H25BrN2O2
M+ 464(100) 466(100)
(A)
C25H25N2O2
m/e 385(13)
(B)
C23H20N2O2
m/e 356(4)
- C2H5
+ H
- Br
-CH2
- C6H4NH
(D)
C15H13NO
m/e 223 (13)
(E)
C20H16BrN2O
m/e 379(3) 381(3)
route a
- C6H5Br
(F)
C14H20N2O
m/e 222 (5)
route c
-CH2
route b
-BrC6H4N=C=NH, -CO
(H)
C19H15BrN2O
m/e 366(3) 368(3)
R.D.A.
-2CH2=CH2
(I)
C15H11BrN2O
m/e 314(6) 316(6)
(G)
C12H9
m/e 153(4)
(L)
C18H14BrN2O
m/e 353(7) 355(5)
-CH2
-CH2
-Br
(O)
C17H11N2O
m/e 259 (3)
-CH2
+ H
+ H
-CH2
(J)
C14H10BrN2O
m/e 301(11) 303(11)
-BrC6H4NH
+ H
(K)
C8H6NO
m/e 132 (3)
(M)
C17H13BrN2O
m/e 340(11) 342(9)
- BrC6H4
-NH - 2H
(N)
C4H7NO
m/e 169 (6)

Table I

Physical, Analytical and PMR Spectral Data of 2′-Substituted Amino-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoles (VII-XV)

Compound No.	State	Mp °C (Crystallization Solvent)	Yield %	Formula	Analyses Calcd./Found C	H	N	UV (ethanol)/UV (ethanol + HCl) λ max (log ε)	PMR (δ) ppm
VII	free base	143-145 (aq ethanol)	90	$C_{25}H_{32}N_2O_2$	76.49 76.15	8.22 8.60	7.14 7.42	248 (4.34), 292 (4.169)/236 (4.342), 283 (4.178)	0.9 (s, 3H, C_{18}-CH_3), 4.72 (s, broad, 1H, NH, disappearing on deuteration), 6.96 (s, 1H, C_4-H), 7.31 (s, 1H, C_1-H)
	picrate	220-222 (a)		$C_{31}H_{35}N_5O_9$	59.89 59.58	5.68 5.94	11.27 11.40		
VIII	free base	137-138 (benzene/ light petr)	91	$C_{26}H_{28}N_2O_2$	77.97 77.98	7.05 7.25	7.00 7.18	248 (4.424), 292 (4.24)/236 (4.425), 283 (4.253)	0.9 (s, 3H, C_{18}-CH_3), 4.67 (s, 2H, $CH_2C_6H_5$), 6.0 (s, broad, 1H, NH, disappearing on deuteration), 7.0 (s, 1H, C_4-H), 7.29 (s, 1H, C_1-H), 7.39 (s, 5H, Ar-H)
	picrate	174-177		$C_{32}H_{31}N_5O_9$	61.04 60.85	4.96 5.32	11.12 11.41		
IX	free base	280-282 (ethanol)	89	$C_{25}H_{26}N_2O_2$	77.69 77.50	6.78 6.90	7.25 7.32	262 (4.467), 302 (4.599)/259 (4.285), 292 (4.486)	
	picrate	233-234		$C_{31}H_{29}N_5O_9$	60.48 60.28	4.75 4.99	11.38 11.60		
X	free base	294-295 (ethanol/ benzene)	75	$C_{26}H_{28}N_2O_2$	77.97 78.02	7.05 7.20	7.00 7.23	264 (4.592), 303 (4.592)/259 (4.313), 293 (4.479)	
	picrate	223-224		$C_{32}H_{31}N_5O_9$	61.04 61.24	4.96 5.05	11.12 11.17		0.92 (s, 3H, C_{18}-CH_3), 2.42 (s, 3H, Tolyl-CH_3) 7.15 (s, 1H, C_4-H), 7.22-7.42 (m, 4H, Ar-H), 7.66 (s, 1H, C_1-H), 9.08 (s, 1H, NH)
XI	free base	255-256 (ethanol/ benzene)	72	$C_{26}H_{28}N_2O_2$	77.97 78.26	7.05 7.21	7.00 7.15	262 (4.532), 301 (4.627)/255 (4.379), 290 (4.514)	0.92 (s, 3H, C_{18}-CH_3), 2.32 (s, 3H, Tolyl-CH_3) 7.1 (s, 1H, C_4-H), 7.22 (d, 2H, J = 8 Hz, Ar-H), 7.45 (s, 1H, C_1-H overlapping with the doublet of Ar-H), 7.52 (d, 2H, J = 8 Hz, Ar-H), 8.26 (s, broad, 1H, NH, disappearing on deuteration)
	picrate	233-235		$C_{32}H_{31}N_5O_9$	61.04 61.30	4.96 5.13	11.12 11.28		
XII	free base	230-232 (ethanol)	71	$C_{26}H_{28}N_2O_3$	74.97 74.82	6.78 7.00	6.73 6.97	262 (4.487), 294 (4.576)/252 (4.305), 288 (4.456)	0.92 (s, 3H, C_{18}-CH_3), 3.35 (s, 3H, OCH_3), 6.98 (d, 2H, J = 8 Hz, Ar-H), 7.1 (s, 1H, C_4-H), 7.45 (s, 1H, C_1-H), 7.56 (d, 2H, J =8 Hz, Ar-H), 8.28 (s, broad, 1H, NH, disappearing on deuteration)

Table I continued

Physical, Analytical and PMR Spectral Data of 2'-Substituted Amino-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoles (VII-XV)

Compound No.	State	Mp °C (Crystallization Solvent)	Yield %	Formula	Analyses Calcd./Found C	H	N	UV (ethanol)/UV (ethanol + HCl) λ max (log ε)	PMR (δ) ppm
	picrate	207-208		$C_{32}H_{31}N_5O_{10}$	59.53 59.23	4.84 4.85	10.85 10.89		
XIII	free base	237-239 (ethanol)	66	$C_{25}H_{25}FN_2O_2$	74.25 74.38	6.18 6.43	6.93 7.19	259 (4.522), 293 (4.581)/256 (4.398), 290 (4.504)	0.90 (s, 3H, C_{18}-CH_3), 7.08 (s, 1H, C_4-H), 6.98-7.18 (m, 2H, Ar-H overlapping with C_4-H), 7.44 (s, 1H, C_1-H), 7.8 (m, 2H, Ar-H), 9.95 (s, 1H, NH, disappearing on deuteration)
	picrate	200-202		$C_{31}H_{28}FN_5O_9$	58.76 58.62	4.42 4.62	11.05 11.09		
XIV	free base	292-293 (ethanol/benzene)	71	$C_{25}H_{25}ClN_2O_2$	71.34 71.49	5.94 6.22	6.65 6.76	266 (4.484), 295 (4.653), 304 (4.653)/263 (4.421), 294 (4.591), 304 (sh) (4.547)	0.90 (s, 3H, C_{18}-CH_3), 7.1 (s, 1H, C_4-H), 7.29 (d, 2H, J = 8 Hz, Ar-H), 7.45 (s, 1H, C_1-H), 7.77 (d, 2H, J = 8 Hz, Ar-H), 10.05 (s, 1H, NH, disappearing on deuteration)
	picrate	192-194		$C_{31}H_{28}ClN_5O_9$	57.27 56.90	4.31 4.50	10.77 11.17		
XV	free base	296-297 (ethanol/benzene)	73	$C_{25}H_{25}BrN_2O_2$	64.51 64.89	5.37 5.68	6.02 5.96	268 (4.525), 296 (4.692), 305 (4.694)/265 (4.479), 295 (4.678), 305 (sh) (4.644)	0.90 (s, 3H, C_{18}-CH_3), 7.02 (s, 1H, C_4-H), 7.4 (d, 2H, J = 8 Hz, Ar-H), 7.41 (s, 1H, C_1-H), 7.65 (d, 2H, J = 8 Hz, Ar-H), 9.64 (s, 1H, NH, disappearing on deuteration)
	picrate	216-118		$C_{31}H_{28}BrN_5O_9$	53.60 53.83	4.03 4.23	10.08 10.03		

(a) All picrate salts were crystallized from ethanol.

pteridine (21) ring was fused to the 3,4-positions of some androstane derivatives, the products possessed contraceptive, antilipogenic (20) and anticancer (21) activities. In view of these observations, we have synthesized some steroidal heterocycles, VII-XXIV, (Scheme I) in which a substituted aminooxazole ring is fused to the 2,3-or 3,4-positions of estrone. This study, consistituting part of an extensive program on the synthesis of modified steroids (22), is aimed at checking the changes in the endocrinological activities caused when the phenolic group as well as the 2- or 4- position of estrone are blocked by an oxazole ring substituted by bulky functional groups. The products were tested *in vitro* for anabolic-catabolic properties by measuring their effects on the activity of bovine pancreatic ribonuclease.

The required compounds, VII-XXIV, were synthesized *via* the routes shown in Scheme I. Estrone (I) was subjected to nitration with concentrated nitric acid and glacial acetic acid and the mixture of 2-nitro (II), 4-nitro (III) and 2,4-dinitroestrone (IV) produced was separated as reported in the literature (23). The mononitro derivatives were reduced by sodium dithionite in alkaline medium to give the 2- and 4-aminoestrone V and VI, respectively, in high yields. The conversion of 2-aminoestrone (V) into the corresponding 2'-substituted amino-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoles (VII-XV) (Scheme 1, Table I) was accomplished by the application of the one-pot cyclodesulfurization reaction (24) recently developed in our laboratory (25). The mixture of the amine V and the selected alkyl, aryl or aralkylisothiocyanate in ethanol was left at room temperature, until all of the amine disappeared (tlc), treated with dicyclohexylcarbodiimide (DCCD) and then heated under reflux until completion of the reaction. The separation of the cyclized products from

Table II

Physical, Analytical and PMR Spectral Data of 2'-Substituted Amino-17-oxoestra-1,5(10),-dieno[4,3-*d*]oxazoles (XVI-XXIV)

Compound No.	State	Mp °C (Crystallization Solvent)	Yield %	Formula	Analyses Calcd./Found C	H	N	UV (ethanol)/UV (ethanol + HCl) λ max (log ε)	PMR (δ) ppm
XVI	free base	227-228 (ethanol/ benzene)	94	$C_{25}H_{32}N_2O_2$	76.49 76.89	8.22 8.35	7.14 7.24	250 (4.384), 286 (4.070)/235 (4.395), 271 (4.005), 278 (4.010)	0.91 (s, 3H, C_{18}-CH_3), 4.85 (d, 1H, NH, disappearing on deuteration), 7.09 (s, 2H, C_1-H + C_2-H)
	picrate	252-254 (a)		$C_{31}H_{35}N_5O_9$	59.89 59.75	5.68 5.88	11.27 11.25		
XVII	free base	192-193 (ethanol/ benzene)	94	$C_{26}H_{28}N_2O_2$	77.97 78.32	7.05 7.26	7.00 7.28	250 (4.361), 286 (4.037)/237 (4.400), 273 (4.005), 280 (4.007)	0.92 (s, 3H, C_{18}-CH_3), 4.74 (s, 2H, -$CH_2C_6H_5$) 5.78 (s, broad, 1H, NH, disappearing on deuteration), 7.09 (s, 2H, C_1-H + C_2-H), 7.4 (s, 5H, Ar-H)
	picrate	256-258		$C_{32}H_{31}N_5O_9$			11.12 11.30		
XVIII	free base	223-224 (ethanol)	96	$C_{25}H_{26}N_2O_2$	77.69 77.59	6.78 6.81	7.25 7.55	268 (4.494), 289 (sh) (4.593), 297 (4.622)/ 259 (4.393), 269 (sh) (4.379), 285 (4.479), 297 (sh) (4.382)	
	picrate	241-242		$C_{31}H_{29}N_5O_9$	60.48 60.08	4.75 5.08	11.38 11.26		
XIX	free base	205-206 (aq ethanol)	98	$C_{26}H_{28}N_2O_2$	77.97 78.23	7.05 7.20	7.00 7.23	268 (4.569), 290 (sh) (4.689), 296 (4.711)/ 258 (4.445), 268 (sh) (4.437), 285 (4.554), 296 (sh) (4.449)	
	picrate	226-228		$C_{32}H_{31}N_5O_9$	61.04 61.13	4.96 5.29	11.12 11.40		
XX	free base	197-198 (aq ethanol)	98	$C_{26}H_{28}N_2O_2$			7.00 6.86	268 (4.425), 291 (4.518), 297 (sh) (4.515)/ 258 (4.301), 284 (4.371)	
	picrate	244-246		$C_{32}H_{31}N_5O_9$	61.04 60.74	4.96 5.27	11.12 11.47		
XXI	free base	198-200 (aq ethanol)	97	$C_{26}H_{28}N_2O_3$	74.97 75.21	6.78 6.82	6.73 6.99	267 (4.528), 289 (4.631)/252 (sh) (4.382), 258 (4.380), 281 (4.472)	0.91 (s, 3H, C_{18}-CH_3), 3.82 (s, 3H, OCH_3), 6.95 (d, 2H, J = 8 Hz, Ar-H), 7.12 (s, 2H, C_1-H + C_2-H), 7.55 (d, 2H, J = 8 Hz, Ar-H), 7.5-7.87 (m, broad, 1H, NH, disappearing on deuteration)

Table II continued

Physical, Analytical and PMR Spectral Data of 2'-Substituted Amino-17-oxoestra-1,5(10),-dieno[4,3-*d*]oxazoles (XVI-XXIV)

Compound No.	State	Mp °C (Crystallization Solvent)	Yield %	Formula	Analyses Calcd./Found C	H	N	UV (ethanol)/UV (ethanol + HCl) λ max (log ε)	PMR (δ) ppm
	picrate	218-220		$C_{32}H_{31}N_5O_{10}$	59.53 59.67	4.84 4.99	10.85 10.81		
XXII	free base	254-255 (ethanol/ benzene)	94	$C_{25}H_{25}FN_2O_2$	74.25 74.05	6.18 6.30	6.93 7.15	265 (4.487), 287 (4.539), 294 (sh) (4.382)/266 (4.369), 284 (4.433)	0.92 (s, 3H, C_{18}-CH_3), 7.01-7.21 (m, 4H, C_1-H + C_2-H + Ar-H), 7.55-7.71 (m, 3H, Ar-H + NH, disappearing on deuteration)
	picrate	237-239		$C_{31}H_{28}FN_5O_9$	58.76 58.62	4.42 4.68	11.05 11.25		
XXIII	free base	258-259 (ethanol/ benzene)	94	$C_{25}H_{25}ClN_2O_2$	71.34 71.70	5.94 6.25	6.65 6.80	269 (4.485), 289 (4.635), 297 (sh) (4.620)/ 261 (4.406), 269 (4.440), 288 (4.574), 297 (sh) (4.527)	0.90 (s, 3H, C_{18}-CH_3), 7.13 (s, 2H, C_1-H + C_2-H), 7.31 (d, 2H, J = 8 Hz, Ar-H), 7.83 (d, 2H, J = 8 Hz, Ar-H), 10.17 (s, 1H, NH, disappearing on deuteration)
	picrate	249-251		$C_{31}H_{28}ClN_5O_9$	57.27 57.16	4.31 4.48	10.77 11.05		
XXIV	free base	262-264 (ethanol/ benzene)	94	$C_{25}H_{25}BrN_2O_2$	64.51 64.59	5.37 5.66	6.02 6.30	270 (4.503), 290 (4.676), 299 (sh) (4.661)/ 262 (sh) (4.424), 270 (4.471), 290 (4.624), 299 (sh) (4.567)	0.90 (s, 3H, C_{18}-CH_3), 7.13 (s, 2H, C_1-H + C_2-H), 7.47 (d, 2H, J = 8 Hz, Ar-H), 7.78 (d, 2H, J = 8 Hz, Ar-H), 10.05 (s, 1H, NH, disappearing on deuteration)
	picrate	247-249		$C_{31}H_{28}BrN_5O_9$	53.60 53.44	4.03 4.20	10.08 10.23		

(a) All picrate salts were crystallized from ethanol.

the final reaction mixtures was dependent on the nature of the substituents in the heterocyclic ring. In the case of aryl derivatives IX-XV, the products were isolated as free bases by concentrating the mixtures and cooling. The other products VII and VIII could not be isolated in a pure state by similar treatment. Consequently, they were separated as the picrate salts and then released into free bases by boiling with alumina and anhydrous sodium carbonate in ethanol. The reaction of 4-aminoestrone (VI) with the selected isothiocyanate derivatives and DCCD, under the same conditions, gave the analogous 2'-substituted amino-17-oxoestra-1,5(10)-dieno[4,3-*d*]oxazoles (XVI-XXIV) (Scheme I, Table II) in high yields. The products were isolated as the picrate salts and then converted into the free bases as mentioned earlier.

The structures of the cyclized products were confirmed by elemental analysis, ir, uv, pmr spectra (Table I and II) and, for representative compounds, by mass spectra. In the ir spectra, the products showed several bands characterizing the N-H, C=N and -C-O-C- stretching vibrations and lacked the absorption band due to the phenolic O-H. The uv spectra (Table I and II) showed two, three or, in some instances, four absorption maxima which underwent hypsochromic shifts on acidification. The pmr spectra (Table I and II) indicated that the N-H proton is attached to the exocyclic nitrogen and as a result resonated at different chemical shifts. It was shown as a singlet at 4.72 in the cyclohexylamino (VII), at 6.00 in the benzylamino (VIII), and at 8.26-8.28 ppm in the *p*-toluidino (XI) and *p*-anisidino (XII) derivatives of the steroidal [2,3-*d*]oxazoles. In the analogous steroidal[4,3-*d*]oxazoles, the same variations in the chemical shift were observed. The N-H hydrogen appeared as a doublet, becoming a singlet on deuteration, at δ 4.85 in the cyclohexylamino (XVI) and as a broad singlet at 5.78 ppm in the benzylamino (XVII) derivatives. In compounds XXI and XXII, it was included in the multiplet of the aromatic protons of the substituents while in compounds XXIII and XXIV, it was shown in the

lower field at 10.05 and 10.17 ppm respectively.

The mass spectrum of 2'-*p*-bromoanilino-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazole (XV) showed the molecular ion peak as the base peak at m/e 464 and 466 (M + 2). Fragmentation of the molecule, according to the pathway 1 (Scheme II), involved the removal of the bromine atom to give ion A at m/e 385. The elimination of ethylene from ring B of such ion followed by dehydrogenation of ring C gave ion B at m/e 356. In accordance with pathway 2, ring D was eliminated from compound XV giving ion C, at m/e 407 (409), which eliminated bromine, methylene and anilino functions to yield ion D at m/e 223. Ion C, after gaining a proton, underwent cleavage of ring C to give ion E at m/e 379 (381). This in turn either eliminated a bromobenzene function giving ion F at m/e 222 (route a), cleaved a *p*-bromophenylcarbodiimide and carbon monoxide moieties to produce ion G at m/e 153 (route b), or underwent successive elimination of methylene groups to yield ions H, L and M at m/e 366 (368), 353 (355) and 340 (342) respectively (route c). Ion H, in turn, underwent a retro Diels-Alder cleavage giving ion I at m/e 314 (316), which on elimination of a methyl ion produced ion J at m/e 301 (303). The removal of a *p*-bromoanilino function from this ion and the acceptance of hydrogen gave ion K at m/e 132. Ion L, on the other hand, successively eliminated bromine and methylene ions to yield ion O at m/e 259. Likewise, the successive removal of *p*-bromophenyl and amino functions from ion M gave ion N at m/e 169. The additional ions due to reported fragments of substituted benzoxazole (26,27) and estrone nuclei (28) were identified.

The products were tested for *in vitro* anabolic-catabolic activities by measuring their effects on the activity of bovine pancreatic ribonuclease. The assays followed the reported procedure of El-Sewedy, *et al.* (29), and the activity of RNAase was calculated according to Sigulem, *et al.* (30). The results revealed that the inclusion of the phenolic function as well as the 2- or 4-position of estrone in an oxazole ring substituted with bulky substituents caused the products to possess almost the same percentage activation as that induced by estrone on the enzyme.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. The ir spectra were measured for Nujol mulls on a Beckmann 4210 infrared Spectrophotometer. The uv spectra were measured for ethanol solutions on Shimadzu double beam UV 200S spectrophotometer. The pmr spectra were recorded on a Perkin-Elmer R-32 Spectrometer. The abbreviations used are: s = singlet, d = doublet, t = triplet and m = multiplet. The mass spectra were measured on AEI Ms-50.

2'-Substituted Amino-17-oxoestra-1(10),4-dieno[2,3-*d*]oxazoles (VII-XV). General Procedure.

Method A. For the Preparation of 2'-Arylamino Derivatives, IX-XV.

2-Aminoestrone (V) (250 mg, 0.87 mmole) was dissolved in hot absolute ethanol (50 ml) and the solution left to cool to room temperature. To this solution was added the appropriate arylisothiocyanate (1 molar equivalent) in absolute ethanol (10 ml) and the clear mixture left to stand at room temperature for 24 hours. A tlc analysis (benzene:ethyl acetate:chloroform; 5:1:5) indicated the disappearance of the amine V. Dicyclohexylcarbodiimide (DCCD) (1.5 molar equivalent) was added and the mixture left at room temperature for 2 hours, heated under reflux for 6 hours, concentrated to about 20 ml and then left to cool overnight at room temperature. The deposited white solid was filtered, dried, weighed and crystallized from the proper solvent giving the great part of the cyclized products IX-XV as free bases. The filtrate was concentrated, treated with picric acid and the product filered, dried, weighed and crystallized from ethanol giving the remainder of the cyclized products as the picrate salt. The yields (Table I) were calculated on both free bases and those derived from picrate salts.

Method B. For the Preparation of 2'-Cyclohexyl (VII) and Benzylamino (VIII) Derivatives.

2-Aminoestrone (V) was reacted with the proper isothiocyanate and DCCD as described above and the final mixtures concentrated when no solid deposited. Therefore, they were treated with picric acid and the picrate salts formed were filtered, dried and crystallized from ethanol. The products were converted into the free bases by stirring the mixture of the picrate salts (500 mg), basic alumina for column chromatography (Prolabo) (5 g) and anhydrous sodium carbonate (350 mg) in refluxing ethanol (50 ml) for 5 hours. Ethanol was completely removed and the wet solid left overnight until completely dry. It was then extracted several times, by decantation, with benzene and the combined benzene decants were filtered and evaporated to dryness. The residue was scratched with light petroleum, filtered, dried and crystallized from the proper solvent. The yields, physical constants, microanalytical, uv and pmr spectral data of the products VII-XV are listed in Table I; ir (Nujol): ν max 3500-3015 (NH), 1745-1720 (C=O), 1675-1635 (C=N), 1610-1570, 1505-1485 (C=C aromatic), 1260-1225 (C-O-C) and 1085-1030 cm^{-1} (C-O-C); ms: for compound X, m/e (relative abundance %): 400 (100), 399 (7), 385 (1), 343 (2), 215 (3), 303 (2), 302 (2), 301 (2), 290 (4), 289 (6), 288 (3), 287 (4), 277 (3), 276 (10), 275 (8), 274 (3), 263 (5), 262 (2), 261 (2), 251 (3), 250 (8), 238 (3), 237 (12), 183 (3), 182 (3), 169 (2), 158 (2), 157 (3), 155 (2), 154 (1), 153 (2), 144 (3), 143 (21), 142 (2), 141 (3), 132 (3), 131 (4), 130 (2), 129 (4), 128 (4), 117 (2), 116 (4), 115 (8), 106 (6), 103 (4), 102 (2), 92 (2), 91 (9), 79 (4), 65 (4), For compound XV: 466 (100), 464 (100), 410 (2), 409 (3), 408 (2), 407 (3), 386 (6), 385 (13), 384 (5), 381 (3), 379 (3), 368 (3), 366 (3), 356 (4), 355 (5), 354 (6), 353 (7), 352 (5), 351 (3), 343 (3), 342 (9), 341 (7), 340 (11), 339 (5), 338 (3), 329 (4), 328 (3), 327 (5), 316 (6), 314 (6), 303 (11), 301 (11), 274 (3), 273 (3), 261 (3), 260 (3), 259 (3), 223 (3), 222 (3), 221 (4), 198 (2), 197 (3), 196 (3), 195 (3), 184 (4), 183 (8), 182 (6), 173 (3), 172 (11), 171 (3), 170 (11), 169 (6), 168 (3), 158 (4), 157 (7), 155 (4), 154 (4), 153 (4), 144 (5), 143 (4), 142 (4), 141 (7), 132 (3), 131 (6), 117 (5), 116 (8), 115 (17), 105 (2), 103 (11), 102 (6), 97 (3), 91 (11), 65 (4).

2'-Substituted Amino-17-oxoestra-1,5(10)-dieno[4,3-*d*]oxazoles (XVI-XXIV). General Procedure.

The mixture of 4-aminoestrone (VI) (250 mg, 0.87 mmole), the appropriate isothiocyanate derivative (1 molar equivalent) and DCCD (1.5 molar equivalent) was reacted in a mixture of absolute ethanol (30 ml) and benzene (15 ml) under the same conditions as for the analogous 2-aminoestrone (V) to give the required cyclised products, XVI-XXIV. They were all separated as the picrate salts and then converted into the free bases as mentioned in method B above. The yields, physical constants, microanalytical, uv and pmr spectral data are recorded in Table II; ir (Nujol): ν max 3540-3120 (NH), 1735-1720 (C=O), 1640-1630 (C=N), 1610-1570, 1500-1485 (C=C aromatic), 1260-1225, (C-O-C) and 1090-1025 cm^{-1} (C-O-C).

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