Steroids. Synthesis of 1,4-Oxazine Derivatives of Estrone

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Estratrieno[3,2-*b*]-1,4-oxazin-3′-one (V) and estratrieno[3,4-*b*]-1,4-oxazin-3′-one (VI) have been converted to the corresponding amidines. The tautomerism of the thiones and the amidines are discussed.

Profound changes in the biological activity of steroids have been observed when a heterocyclic ring is attached to the steroid nucleus (1). A variety of steroidal heterocycles (2) derived from estratriene have been reported (3). Although estratrieno-1,3-oxazines have been prepared, the synthesis of the isomeric estratrieno-1,4-oxazines has not been reported. Of the two methods for the construction of 1,4-benzoxazines (4a), the route through the *o*-nitrophenoxy acetic acid or a variant (4b) thereof offers greater flexibility in the choice of substituents at positions 2 and 3 of the oxazine ring.

An attempt was made to condense 2-nitro and 4-nitroestrones (5) with chloroacetic acid, but the results were not encouraging. The desired estrone ethers (I) and (II) were obtained in very low yields. As a result, the second method of synthesis was then tried. 2-Amino and 4-aminoestrones (6) were condensed with chloroacetyl chloride to yield the respective chloroamides (III) and (IV) in good yields. Ring closure of the amides to the corresponding oxazine derivatives (V) and (VI) was effected by methanolic potassium hydroxide. Sodium borohydride reduction of (V) and (VI) yielded the corresponding steroidal 17β-alcohols (VII) and (XXI) respectively.

In order to carry out modification on the oxazine rings, it was necessary to protect the C-17 hydroxyl group. Treatment of (VII) with dihydropyran yielded the 17-tetrahydropyranyloxy steroid (VIII), but in a poor yield. Acetylation with acetic anhydride and pyridine at room temperature of the alcohols (VII) and (XXI) gave the corresponding 17β-acetates (X) and (XXII). However, when acetylation of (VII) was carried out at an elevated temperature, a diacetyl compound was obtained. The nmr spectrum of the product showed two low field methyl signals as sharp singlets at δ 2.06 ppm and δ 2.68 ppm. Its ir spectrum had carbonyl absorptions at 1802 cm^{-1} and 1728 cm^{-1} (sh). The nmr signal at δ 2.06 ppm and ir band at 1728 cm^{-1} could be ascribed to the C-17 acetyl function. Although *N*-acetylation of cyclic lactams is known to occur (7), such a possibility appeared to be unlikely because the ir band at 1802 cm^{-1} seemed too high for the imide group (8). The LAH reduction of the diacetyl compound gave XXXII, which could also be obtained from the LAH reduction of V. Although the formation of XXXII implied the absence of an imide linkage in the diacetyl compound, its presence could not be completely ruled out as the cleavage of a C-N bond of an imide by LAH has been reported to occur (9). However, when a solution of the diacetyl compound was filtered through alumina, the monoacetyl product X was obtained. This transformation is analogous to the loss of the acetyl group from a phenolic acetate (10) when the latter is similarly treated on alumina. Hence, the diacetyl compound is the imidic anhydride IX, which has been postulated as an intermediate in the conversion of amides to imides (11). Although the isolation of acetylimidic anhydrides from amides has not been reported to date, except in the case of cyclic hydrazides (13), the isolation of methoxyformyl and benzoyl anhydrides of amides and their thermal rearrangement to the corresponding imides are known (12). The imidic anhydride IX upon reaction with phosphorus pentasulfide in pyridine lost the imidoyl acetyl group and yielded the thiolactam XI. The latter compound, however, could be prepared more conveniently from the amide X under similar conditions.

With a view to converting the amide X into amidines, several attempts were made to prepare the imidate XIII with Meerwein's reagent (14). This reagent has been used extensively to prepare imidates from amides (15) and thioimidates from thiolactams (14). Conversion of these imidates to amidines has been applied to simple 1,4-oxazine (17) and 1,4-thiazine (16) systems. The lactam X was allowed to react with excess Meerwein's reagent for a prolonged period of time in order to achieve completion of the reaction as determined by tlc. Work up of the reaction mixture yielded the starting material and the imidate XIII, which could be separated by crystallization. The structure XIII assigned to the imidate is supported by the presence of a two-proton singlet at δ 4.47 ppm in

the nmr spectrum due to the methylene protons of the oxazine ring and a band at 1660 cm^{-1} due to C=N group in the ir spectrum. A similar reaction of the thiolactam XI gave the lactam X as the only crystalline material isolated. This substance probably resulted from the hydrolysis (18) of the intermediate thioimidate. The thioimidate XII was readily prepared from XI with potassium hydroxide and methyl iodide (19). The amidines XIV-XX were obtained by reaction of the thioimidate XII with the appropriate amines. The amidines produced stable hydrochloride salts. Hydrolysis of the 17β-acetoxy group in these compounds could be readily accomplished with sodium carbonate without affecting the amidine linkage. This is exemplified by the conversion of XVI to XVIa.

An analogous series of reactions was carried out with the lactam XXII. The reaction of XXII with phosphorus pentasulfide in pyridine gave the thiolactam XXIII, which was converted to the thioimidate XXIV. This substance in turn reacted with the appropriate amines to yield the amidines XXV-XXXI. The *N'*,*N'*-disubstituted amidines XXV-XXVIII formed stable monohydrochlorides whereas those XXIX-XXXI with *N'*-monosubstitution were found to be very labile to acid, and attempts to crystallize the semisolid oxalate or hydrochloride salts resulted in the hydrolysis of the amidine group to regenerate the lactam XXII. The LAH reduction of VI yielded the oxazine derivative XXXVII.

N-Alkylation of the amides was also attempted. Reaction of X with 2-diethylaminoethyl chloride and 2-diisopropylaminoethyl chloride in the presence of sodium hydride yielded the *N*-substituted lactams XXXIII and XXXIV, respectively. However, all attempts to react X with 3-diethylaminopropyl chloride failed. The LAH reduction of XXXIII gave the oxazine derivative XXXV. However, reduction of XXXIV with LAH yielded an unstable base XXXVI which underwent rapid decomposition in the presence of hydrochloric acid to give a very small amount of a solid monohydrochloride salt. The alkylation of the lactam nitrogen in XXII with 2-diethylaminoethyl chloride proceeded with difficulty. Only under forcing conditions could a small amount of an *N*-alkylated product be isolated. The nmr (20) spectrum was found to be consistent with a mixture of the 17β-acetoxy and 17β-hydroxy lactams XXXVIII. The nmr spectrum showed two 18-methyl signals at δ 0.73 ppm and δ 0.83 ppm for the 17β-hydroxy and 17β-acetoxy steroids and two signals for the methylene groups in the oxazine ring at δ 4.35 ppm and δ 4.46 ppm as singlets. The ir spectrum showed hydroxy absorptions at 3700 cm^{-1} and 3620 cm^{-1}.

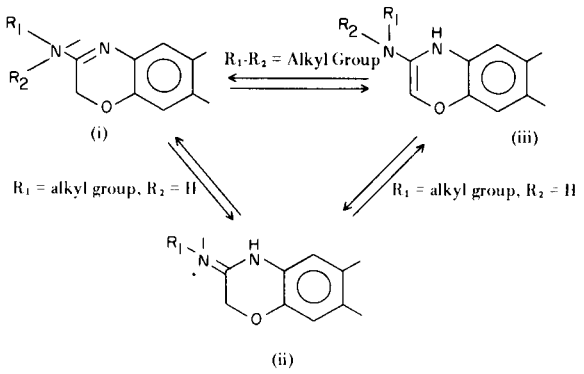
Prototropy.

Thioamides XI and XXIII.

Studies on the thiol-thione tautomeric equilibrium of thioamides (21) by uv and ir spectroscopy have shown that the thioamides exist predominantly in the thione form. Recent studies (22) on the tautomerism of simple benzoxazine-3-thione have established that the thioamide group in this class of compounds also exists in the thione form. The steroidal thiolactams are no exception. The uv spectra of the thioamide XI is different from that of the corresponding methyl thioimidate XII. Similar differences in the uv spectra are also observed between the thiolactam XXIII and the thioimidate XXIV. The nmr spectra of the thioamides and the thioimidates show sharp two-proton singlets in the region of δ 4-5 ppm, which are attributable to the methylene protons in the oxazine ring. Thus, the possibility of enolization involving the C_2-atom of the heterocyclic ring in all these compounds is excluded.

Amidines XIV-XX and XXV-XXXI.

Voluminous studies on the amino-imino tautomerism in heteroaromatic amines have been made (23). However, comparatively very little work on the tautomerism of aliphatic amidines has been recorded (24). As in the case of the benzoxazine-3-thiones, there exist three possible tautomeric forms (i), (ii) and (iii) for the amidines:

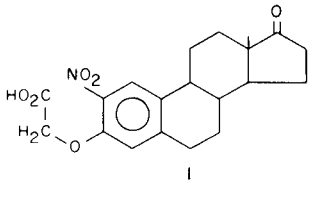


Participation of the form (iii) in the tautomeric equilibrium of both the *N'*-monosubstituted and the *N'*,*N'*-disubstituted amidines is excluded since all the compounds show in their ir spectra strong C=N band (25) at 1550 cm^{-1} to 1630 cm^{-1} and their nmr spectra show two-proton signals as sharp singlets in the region of δ 4.3-4.6 ppm for the C_2-methylene group in the oxazine ring. The existence of the *N'*,*N'*-disubstituted amidines in the form (i) is thus confirmed. The equilibrium of the forms (i) and (ii) for the *N'*-monosubstituted amidines was next considered. In the nmr spectra of the estratrieno [3,2-*b*]-1,4-oxazine derivatives XII, XIII and XIV-XVI, in which the double bonds are endocyclic, the C_1-aromatic

protons appear at a lower field (about 0.3 ppm) and the C_4-aromatic protons appear at a higher field (about 0.1 ppm) than the corresponding protons in the compounds in which the double bonds are exocyclic V, VIII, X and XI) (Table I). The C_1 and C_4-aromatic protons in the *N'*-monosubstituted amidines have identical chemical shifts (Table III) to those compounds with endocyclic double bonds. This suggests that the *N'*-monosubstituted amidines also have endocyclic double bonds and exist in form (i). Confirmatory evidence of the presence of endocyclic double bonds in the *N'*-monosubstituted amidines is obtained from the uv spectra of these compounds which are very similar to those of the *N',N'*-disubstituted amidines. The amidines in the 3,4-*b* series also have an endocyclic double bond because their uv spectra are identical with those of the corresponding compounds in the 3,2-*b* series. Figure 1 shows representative comparisons of the uv spectra of the amidines belonging to the [3,2-*b*] and [3,4-*b*] series.

TABLE I

Compounds with exocyclic double bonds	Chemical shifts of the aromatic protons (δ): C_1	C_4
V	6.77	6.71
VIII	6.74	6.70
X	6.78	6.70
XI	6.9	6.70
Compounds with endocyclic double bonds		
XII	7.22	6.61
XIII	7.08	6.60
XIV	7.03	6.55
XVI	7.0	6.57



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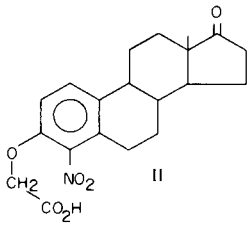

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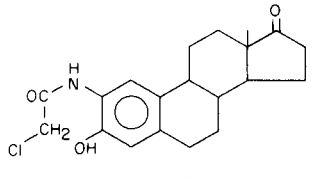

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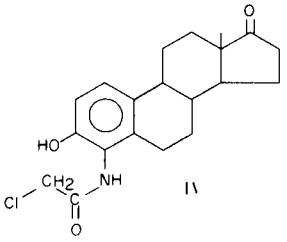

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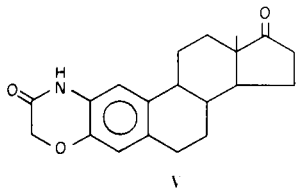

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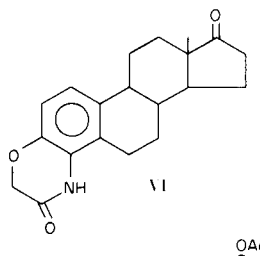

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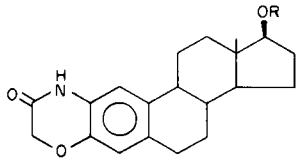
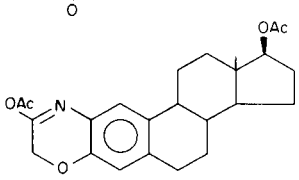


VII R = H

VIII R =



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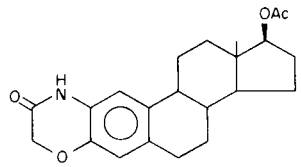
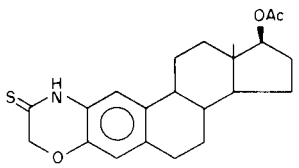


X



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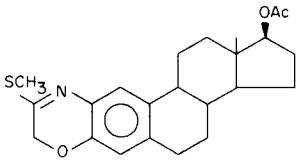
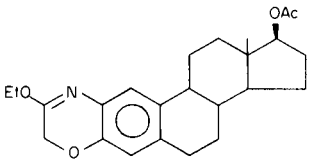
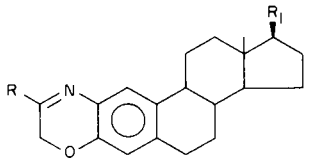


XII



XIII



XIV R = -N , R_1 = OAc

XV R = -N , R_1 = OAc

XVI R = -N O, R_1 = OAc

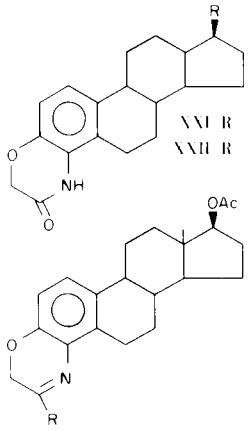
XVIa R = -N O, R_1 = OH

XVII R = -N N-CH_3, R_1 = OAc

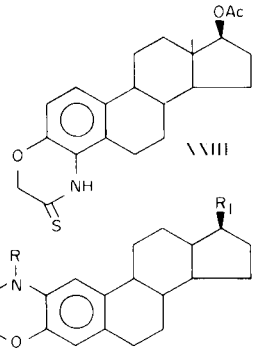
XVIII R = -$NH(CH_2)_2N(Et)_2$, R_1 = OAc

XIX R = -$NH(CH_2)_3N(Et)_2$, R_1 = OAc

XX R = -$NH(CH_2)_4N(Me)_2$, R_1 = OAc



XXI R OH
XXII R OAc



XXIII

XXIV R SCH_3

XXV R -N

XXVI R -N

XXVII R -N O

XXVIII R -N N-CH_3

XXIX R $-NH(CH_2)_2N(Et)_2$

XXX R $-NH(CH_2)_3N(Et)_2$

XXXI R $-NH(CH_2)_4N(Me)_2$

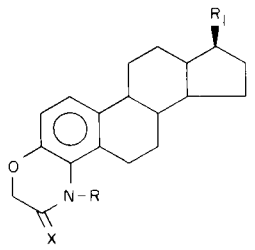
XXXII, X = H_2, R H, R_1 OH

XXXIII, X O, R $-(CH_2)_2N(Et)_2$, R_1 OAc

XXXIV, X O, R $-(CH_2)_2N(Pr^i)_2$, R_1 OAc

XXXV, X H_2, R $-(CH_2)_2N(Et)_2$, R_1 OH

XXXVI, X H_2, R $-(CH_2)_2N(Pr^i)_2$, R_1 OH



XXXVII, X H_2, R H, R_1 OH

XXXVIII, X O, R $-(CH_2)_2N(Et)_2$, R_1 OH and OAc

EXPERIMENTAL

Nmr spectra were determined for deuteriochloroform solutions at 60 MH_z with TMS as internal standard and the chemical shifts are expressed in δ-values (ppm) down field from TMS (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad). Unless otherwise specified ir and uv spectra were determined respectively for chloroform and methanol solutions. Melting points were taken in capillaries and are uncorrected. Alumina refers to Woelm neutral, grade I. Anhydrous sodium sulfate was used for drying solvents.

(2-Nitro-17-oxoestra-1,3,5(10)-trien-3-yl)oxyacetic Acid (I).

2-Nitroestrone (1 g.) in dioxane (5 ml.) was treated with sodium hydroxide (115 mg.). To the resulting solution was added chloroacetic acid (285 mg.) in water (1 ml.) containing sodium carbonate (160 mg.). The mixture was refluxed for three hours and diluted with water (100 ml.). The slightly alkaline solution was filtered and acidified with concentrated hydrochloric acid. The precipitated solid (140 mg.) crystallized from methanol (charcoal) as yellow flakes (110 mg.), m.p. 253-255° dec.; ir (potassium bromide, cm^{-1}): 3400-2500, 1760, 1709, 1515, 1342, 1190, 1058; nmr ($DMSO^{d-6}$): 0.83 (3H,s), 4.82 (2H,s), 6.98 (1H,s), 7.72 (1H,s).

Anal. Calcd. for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.13; H, 6.29; N, 3.67.

(4-Nitro-17-oxoestra-1,3,5(10)-trieno-3-yl)oxyacetic Acid (II).

The brown solution of 4-nitroestrone (3.02 g.) in water (50 ml.) containing sodium hydroxide (0.4 g.) was treated with a solution of chloroacetic acid (1.1 g.) in water (50 ml.) containing sodium carbonate (0.75 g.). The mixture was refluxed for 18 hours and acidified with concentrated hydrochloric acid. The precipitate was washed with water and extracted with sodium carbonate (1% aq.). The aqueous solution was acidified with concentrated hydrochloric acid and the precipitate was triturated with methanol when a solid (0.7 g.), m.p. 294-298° dec. was obtained. It crystallized from methanol (charcoal) as colorless flakes (630 mg.), m.p. 293-294° dec.; ir (potassium bromide, cm^{-1}): 3300-2500, 1762, 1725, 1538, 1290, 1198; nmr ($DMSO^{d-6}$): 0.83 (3H,s), 4.80 (2H,s), 7.25 (2H,q).

Anal. Calcd. for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: C, 64.32; H, 6.29; N, 3.71.

2-(2-Chloroacetamido)-3-hydroxyestra-1,3,5(10)-trien-17-one (III).

To a solution of 2-aminoestrone (6) (3.2 g.) in dry chloroform (150 ml.) was slowly added a solution of chloroacetyl chloride (1.3 g.) in chloroform (50 ml.) and the mixture was refluxed for 22 hours. The dark solution was filtered from insoluble residue and then concentrated. The oily residue crystallized from methanol (charcoal) as colorless needles (2.7 g.), m.p. 158-166°. Further crystallization from methanol gave colorless needles (2.2 g.), m.p. 193° dec. (sintering at 181°); ir (cm^{-1}): 3584, 3356, 1740, 1667, 1261; nmr ($DMSO^{d-6}$): 0.82 (3H,s), 4.77 (2H,s), 6.6 (1H,s), 7.8 (1H,s).

Anal. Calcd. for $C_{20}H_{24}ClNO_3$: C, 66.37; H, 6.68; N, 3.87. Found: C, 66.32; H, 6.91; N, 3.74.

4-(2-Chloroacetamido)-3-hydroxyestra-1,3,5(10)-trien-17-one (IV).

A suspension of 4-Aminoestrone (6) (0.8 g.) in chloroform (200 ml.) was refluxed and to it was added a solution of chloroacetyl chloride (0.4 g.) in chloroform (20 ml.) and the mixture was refluxed for 4 hours. The chloroform solution was filtered and the solvent removed. The residue upon treatment with chloroform-ether gave a pale yellow solid (0.8 g.), m.p. 188-192° which upon several crystallizations from the same solvent mixture (charcoal) yielded colorless needles (0.71 g.), m.p. 192-193°; ir (cm^{-1}): 3368, 1740, 1653; nmr ($DMSO^{d-6}$): 0.75 (3H,s), 4.18 (2H,s), 6.88 (2H,q).

Anal. Calcd. for $C_{20}H_{24}ClNO_3$: C, 66.38; H, 6.99; N, 3.87. Found: C, 66.20; H, 6.85; N, 3.68.

2′,4′-Dihydro-17-oxoestra-1,3,5(10)-trieno[3,2-*b*]-1′,4′-oxazin-3′-one (V).

To a warm solution of III, (1.59 g.) in methanol (70 ml.) was added a solution of potassium hydroxide (0.2 g.) dissolved in a small amount of water. The mixture was warmed on steam-bath for 5 minutes and then diluted with water (250 ml.). The precipitate was dissolved in chloroform and the solution after drying was filtered through alumina (30 g.) and eluted with chloroform (200 ml.). The solid obtained upon removal of the solvent crystallized from methanol (charcoal) as colorless needles (1.1 g.), m.p. 239-242° dec.; ir (cm^{-1}): 3400, 1740, 1700, 1065, 1040; nmr 0.91 (3H,s), 4.58 (2H,s), 6.71 (1H,s), 6.77 (1H,s); uv: 259, 291 mμ (log ε 3.81, 3.72).

TABLE II

Amidine	Thioimidate (amount)	Amine (amount)	Reaction Time	Solvent of Crystallization	M.p.	Yield	Found %	Calcd. for
XIV	XII (1.4 g.)	Pyrrolidine (0.3 g.)	48 hours	Methanol	235-237°	83%	C, 74.20 H, 8.45 N, 6.50%	$C_{26}H_{34}N_2O_3$: C, 73.90 H, 8.11 N, 6.63%
XV	XII (1.37 g.)	Piperidine (0.35 g.)	108 hours	Ether:hexane	174-175°	80%	C, 74.23 H, 8.23 N, 6.18%	$C_{27}H_{36}N_2O_3$: C, 74.28 H, 8.31 N, 6.42%
XVI	XII (1.4 g.)	Morpholine (0.34 g.)	96 hours	Methanol	178-181°	78%	C, 71.35 H, 7.94 N, 6.34%	$C_{26}H_{34}N_2O_4$: C, 71.20 H, 7.82 N, 6.39%
XVII	XII (1.3 g.)	*N*-Methylpiperizine (0.4 g.)	72 hours	Ether:hexane	209-210° dec.	54%	C, 72.03 H, 8.43 N, 9.23%	$C_{27}H_{37}N_3O_3$: C, 71.81 H, 8.26 N, 9.31%
XVIII	XII (1.3 g.)	2-Diethylamino-ethylamine (0.38 g.)	48 hours	Ether:hexane	151-152°	67%	C, 72.19 H, 9.05 N, 8.90%	$C_{28}H_{41}N_3O_3$: C, 71.91 H, 8.84 N, 8.99%
XIX	XII (1.2 g.)	3-Diethylamino-propylamine (0.45 g.)	72 hours	Hexane	127-129°	68%	C, 71.87 H, 8.99 N, 8.50%	$C_{29}H_{43}N_3O_3$: C, 72.31 H, 9.0 N, 8.72
XX	XII (1.2 g.)	4-Dimethylamino-butylamine (0.42 g.)	112 hours	Hexane	116-117°	84%	C, 71.60 H, 8.83 N, 9.08%	$C_{28}H_{41}N_3O_3$: C, 71.91 H, 8.84 N, 8.99%
XXV	XXIV (1.5 g.)	Pyrrolidine (0.35 g.)	136 hours	Dichloromethane: ether	204-206°	76.2%	C, 73.80 H, 8.11 N, 6.94%	$C_{26}H_{34}N_2O_3$: C, 73.90 H, 8.11 N, 6.63%
XXVI	XXIV (1.2 g.)	Piperidine (0.3 g.)	192 hours	Methanol	148-150°	69%	C, 74.51 H, 8.37 N, 6.34%	$C_{27}H_{36}N_2O_3$: C, 74.28 H, 8.31 N, 6.42%
XXVII	XXIV (1.5 g.)	Morpholine (0.36 g.)	70 hours	Dichloromethane: ether	189-190°	90%	C, 71.47 H, 8.04 N, 6.49%	$C_{26}H_{34}N_2O_4$: C, 71.20 H, 7.82 N, 6.39%
XXVIII	XXIV (1.5 g.)	*N*-Methylpiperizine (0.5 g.)	72 hours	Dichloromethane: ether	150-151°	85.7%	C, 71.78 H, 8.48 N, 9.33%	$C_{27}H_{37}N_3O_3$: C, 71.81 H, 8.26 N, 9.31%
XXIX	XXIV (1.5 g.)	2-Diethylamino-ethylamine (0.8 g.)	108 hours	Hexane - pentane	115.5-116.5°	71.2%	C, 72.29 H, 9.03 N, 8.89%	$C_{28}H_{41}N_3O_3$: C, 71.91 H, 8.84 N, 8.99%
XXX	XXIV (1.8 g.)	3-Diethylamino-propylamine (0.65 g.)	260 hours	Moist Hexane	175° (softens at 171°)	55.7%	C, 72.07 H, 9.15 N, 8.67%	$C_{29}H_{43}N_3O_3$: C, 72.31 H, 9.00 N, 8.72%
XXXI	XXIV (2.1 g.)	4-Dimethylamino-butylamine (0.68 g.)	240 hours	Moist Hexane	91-95° (softens at 80°)	59.4%	C, 71.78 H, 9.05 N, 8.91%	$C_{28}H_{41}N_3O_3$: C, 71.91 H, 8.84 N, 8.99%

TABLE III

Amidine	Uv mμ (log ε) sh = shoulder	Ir (cm^{-1})	Nmr (δ) s = singlet, d = doublet, t = triplet, q = quartet, b = broad, m = multiplet
XIV	238sh (4.32), 246 (4.19), 282sh (4.17), 293 (4.21), 309.5 (4.18)	1730, 1625, 1580, 1250, 1040	0.82 (3H, s), 2.09 (3H, s), 4.58 (2H, s), 4.5-4.9 (1H, b), 6.55 (1H, s), 7.03 (1H, s)
XV	226.5 (4.37), 238 (4.33), 247sh (4.21), 284sh (4.23) 294 (4.28), 310 (4.27)	1732, 1626, 1580, 1258, 1020	0.83 (3H, s), 2.05 (3H, s), 4.58 (2H, s), 4.5-4.9 (1H, b), 6.55 (1H, s), 7.02 (1H, s)
XVI	226 (4.29), 247sh (4.12), 283sh (4.11), 293 (4.16), 309.5 (4.13)	1730, 1625, 1580, 1250, 1030	0.81 (3H, s), 2.03 (3H, s), 4.58 (2H, s), 4.5-4.9 (1H, b), 6.57 (1H, s), 7.0 (1H, s)
XVII	227 (4.28), 238 (4.25) 241.5sh (4.13), 283sh, (4.13), 293 (4.17), 310 (4.15)	1730, 1630, 1585, 1265, 1035	0.82 (3H, s), 2.03 (3H, s), 2.3 (3H, s), 4.58 (2H, s), 4.5-4.9 (1H, b), 6.57 (1H, s), 7.03 (1H, s)
XVIII	223 (4.32), 234sh (4.24), 242sh (4.07), 277sh, (4.04), 285 (4.14) 301 (3.98)	3400, 1725, 1630, 1600, 1250, 1030	0.8 (3H, s), 1.0 (6H, t), 2.05 (3H, s), 2.55 (6H, q), 3.48 (2H, t), 4.35 (2H, s), 4.5-5.0 (1H, b), 6.55 (1H, s), 7.04 (1H, s)
XIX	223 (4.37), 232sh (4.32), 2.41sh (4.12), 277 (4.07), 285 (4.08), 301 (4.01)	3440, 3200, 1725, 1630, 1595, 1260, 1040	0.83 (3H, s), 1.03 (6H, t), 2.03, (3H, s), 2.54 (6H, q), 3.57 (2H, t), 4.3 (2H, s), 4.5-5.0 (1H, b), 6.55 (1H, s), 7.05 (1H, s)
XX	223 (4.40), 232sh (4.32), 241sh (4.31), 277 (4.11), 285 (4.12), 301 (4.06)	3450, 3230, 1730, 1630, 1600, 1265, 1040	0.83 (3H, s), 2.07 (3H, s), 2.23 (6H, s), 3.45 (2H, t), 4.33 (2H, s) 6.57 (1H, s), 7.0 (1H, s)
XXV	230 (4.32), 235 (4.31), 244sh (4.17), 283sh (4.16), 293 (4.19), 3.08 (4.17)	1730, 1610, 1570, 1260, 1035	0.82 (3H, s), 2.03 (3H, s), 3.5 (4H, t), 4.52 (2H, s), 4.5-5.9 (1H,b) 6.72 (2H, q)
XXVI	231 (4.30), 236 (4.32), 245sh (4.16), 285sh (4.17), 295sh (4.23), 318sh (4.18)	1725, 1610, 1565, 1255, 1030	0.82 (3H, s), 2.03 (3H, s), 3.5 (4H, m) 4.55 (2H, s), 4.55-4.95 (1H, b), 6.73 (2H, q)
XXVII	230 (4.29), 235.5 (4.30), 245sh (4.15), 285sh (4.15), 294 (4.18), 312sh (4.06)	1730, 1615, 1575, 1260, 1040	0.82 (3H, s), 2.03 (3H, s), 4.55 (2H, s), 3.68 (8H, m), 4.45-4.95 (1H, b), 6.73 (2H, q)
XXVIII	231 (4.25), 236 (4.24), 254sh (4.08), 285sh (4.08), 295 (4.11), 310 (4.02)	1720, 1605, 1565, 1255, 1030	0.82 (3H, s), 2.05 (3H, s), 2.47 (3H, s), 3.59 (4H, t), 4.57 (2H, s), 4.5-4.9 (1H, b), 6.76 (2H, q)
XXIX	226 (4.38), 232sh (4.36), 241sh (4.17), 282 (4.08), 304sh (3.95)	3460, 3415, 1730, 1625, 1570, 1265, 1035	0.82 (3H, s), 1.03 (6H, t), 2.08 (3H, s), 2.56 (6H, q), 3.53 (2H, t), 4.33 (2H, s), 4.5-5.2 (1H, b), 6.8 (2H, q)
XXX	226 (4.39), 231.5sh (4.36), 241sh (4.15), 282 (4.11), 304sh (3.95)	3460, 3240, 1730, 1630, 1580, 1255, 1035	0.82 (3H, s), 1.03 (6H, t), 2.05 (3H, s), 2.53 (6H, q), 3.53 (2H, t), 4.56 (2H, s), 4.5-5.0 (1H, b), 6.76 (2H, q)
XXXI	226.5 (4.38), 232 (4.35), 240 (4.16), 282 (4.12), 304 (3.97)	3450, 3240, 1725 1630, 1570, 1255, 1030	0.82 (3H, s), 2.05 (3H, s), 2.23 (6H, s), 3.42 (2H, t), 4.58 (2H, s), 4.5-5.0 (1H, b), 6.76 (2H, q)

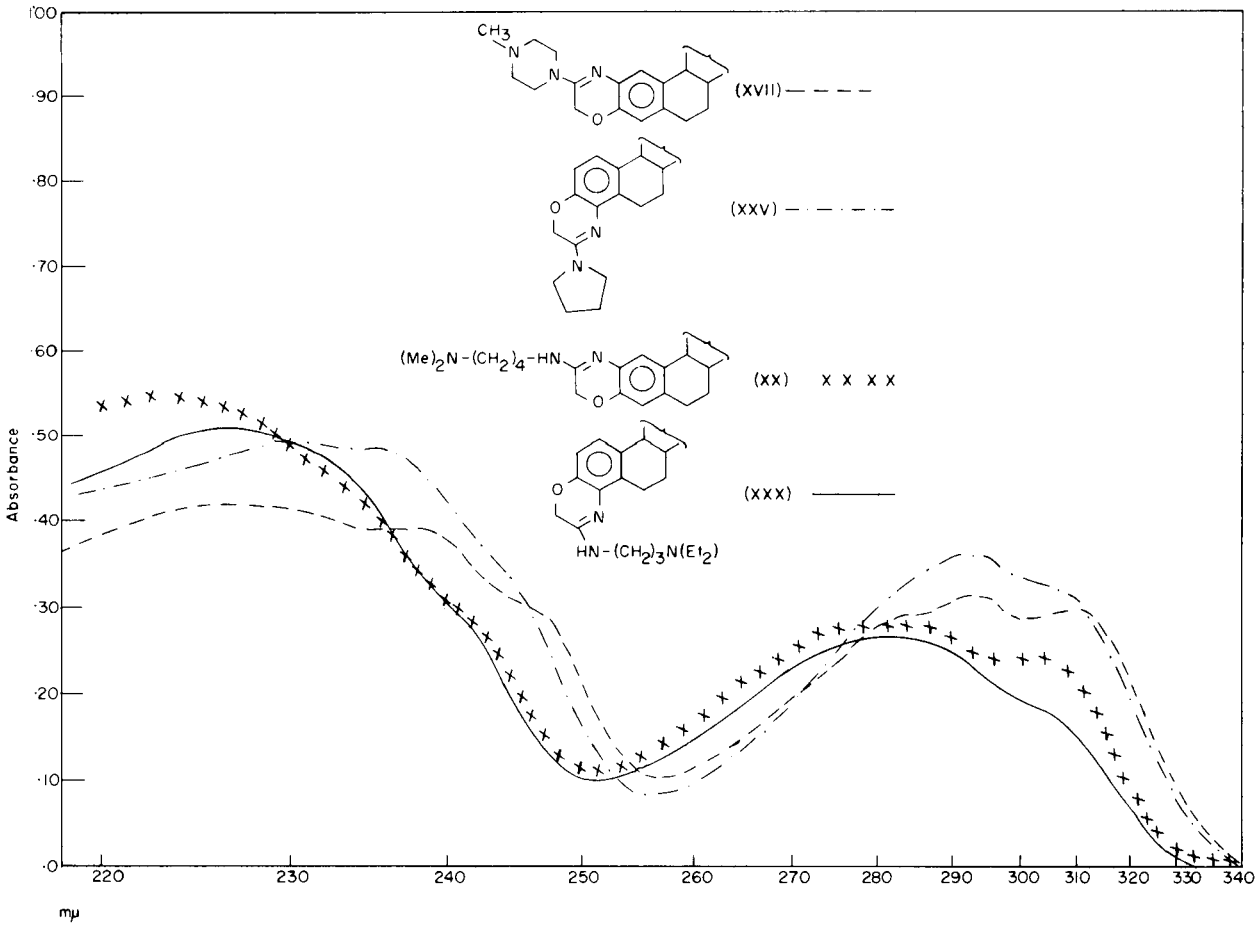


Figure 1

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.70; H, 7.25; N, 4.28.

2′,4′-Dihydro-17-oxoestra-1,3,5(10)-trieno[3,4-*b*]-1′,4′-oxazin-3′-one (VI).

A solution of IV (0.8 g.) in hot methanol (30 ml.) was treated with a solution of potassium hydroxide (90 mg.) in methanol (5 ml.) and the mixture was heated on steam-bath for 1 minute and left at room temperature for 2 hours. The precipitate, obtained on dilution of the solution with water (150 ml.), crystallized from methanol (charcoal) as colorless needles (0.63 g.), m.p. 305-306° dec.; ir (potassium bromide,cm^{-1}): 3200, 1741, 1695; nmr: 0.92 (3H,s), 4.57 (2H,s), 6.87 (1H,s), 6.93 (1H,s); uv ($CHCl_3$-MeOH): 257.5, 291 mμ (log ε 3.80, 3.42).

Anal. Calcd. for $C_{20}H_{23}NO_3$: C, 73.82; H, 7.12; N, 4.30. Found: C, 73.73; H, 7.11; N, 4.26.

2′,4′-Dihydro-17β-hydroxyestra-1,3,5(10)-trieno[3,2-*b*]-1′,4′-oxazin-3′-one (VII).

A solution of V (3 g.) in methanol (400 ml.) at 40-50° was treated with sodium borohydride (1.5 g.) and the solution was stirred at 40-50° for 2.5 hours. The solvent was removed and the residue was treated with water (300 ml.) and acidified with glacial acetic acid. The resulting solid (3 g.) had m.p. 280-286° dec. Crystallization of this material (0.5 g.) from methanol gave colorless needles (0.48 g.) m.p. 287-289° dec.; ir (potassium bromide cm^{-1}): 3559, 3125, 1684, 1212, 1036; uv: 258, 292 mμ (log ε 3.81, 3.72).

Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.46; H, 7.80; N, 4.28.

2′,4′-Dihydro-17β-tetrahydropyranyloxy-1,3,5(10)-trieno[3,2-*b*]-1′,4′-oxazin-3′-one (VIII).

A solution of (VII) (0.32 g.) in dry dichloromethane (75 ml.) was treated with dihydropyran (0.1 g.) and a crystal of *p*-toluenesulfonic acid. The mixture was left at room temperature overnight. The solution was washed with water, dried and the solvent was removed. The residue was chromatographed on alumina and eluted with benzene followed by chloroform. The chloroform eluate (0.24 g.) was found to contain some starting material (tlc, silica-chloroform:ethyl acetate 3:1). This was repeatedly crystallized from methanol when colorless needles (55 mg.), m.p. 241-243° dec. were obtained; ir (potassium bromide,cm^{-1}): 3300-3050, 1692; nmr: 0.82 (3H,s), 4.55 (2H,s), 4.5-4.8 (1H,b), 6.7 (1H,s), 6.74 (1H,s).

Anal. Calcd. for $C_{25}H_{33}NO_4$: C, 72.96; H, 8.08; N, 3.40. Found: C, 72.94; H, 8.08; N, 3.34.

Acetylation of VII.

(i) A solution of VII (0.2 g.) in pyridine (2 ml.) and acetic

anhydride (2 ml.) was allowed to stand at room temperature for 7.5 hours and then treated with ice-water. The precipitate (0.21 g.), m.p. 253-262° dec. crystallized from methanol (charcoal) to give colorless needles of X (0.18 g.) m.p. 268-270° dec.; ir (potassium bromide, cm^{-1}): 3400, 1724, 1515, 1266, 1010; nmr: 0.83 (3H,s), 4.58 (2H,s), 6.70 (1H,s), 6.78 (1H,s); uv: 259, 295 mμ (log ε 3.81, 3.72).

Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.53; H, 7.29; N, 3.62. Found: C, 71.53; H, 7.29; N, 3.62.

(ii) The alcohol VII (1.5 g.) in pyridine (20 ml.) and acetic anhydride (12 ml.) was heated on steam-bath for 7.5 hours. The brown reaction mixture was cooled and treated with ice-water. The precipitated solid crystallized from methanol (charcoal) to give IX as colorless needles (0.89 g.), m.p. 171-172°; ir (potassium bromide, cm^{-1}): 1802, 1728sh, 1700, 1563, 1070; nmr: 0.82 (3H,s), 2.05 (3H,s), 2.68 (3H,s), 4.51 (2H,s), 6.74 (1H,s), 7.54 (1H,s); uv: 233, 285 mμ (log ε 3.80, 3.52).

Anal. Calcd. for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 70.22; H, 7.16; N, 3.34.

Conversion of the Diacetyl Compound IX to the Monoacetate X.

A solution of the diacetyl compound IX (0.1 g.) in benzene was added to a column of alumina (20 g.) and eluted with chloroform (400 ml.) followed by chloroform-methanol (5%) mixture (200 ml.). The combined solid (70 mg.), m.p. 255-264°, obtained upon evaporation of the solvents crystallized from methanol as colorless needles (62 mg.), m.p. 265-268° dec. The product was found to be identical with the monoacetyl compound X by mixed m.p. determination and ir comparison.

3′-(Ethoxy)-17β-acetoxyestra-1,3,5(10)-trieno[3,2-*b*]-2′H-1′,4′-oxazine (XIII).

A solution of the lactam X (0.37 g.) in dry dichloromethane was treated with triethyloxonium fluoroborate (0.5 g.) and the mixture was stirred for 3.5 hours when tlc showed complete absence of starting material. The reaction mixture was cooled in ice-bath and treated with a solution of potassium carbonate (50%) and stirred for ½ hour. The organic layer was separated, washed with water, dried and evaporated. The oily residue, which was now found to contain starting material (tlc) was extracted with hot hexane (25 ml.). The insoluble solid (120 mg.), m.p. 256-261° dec. was found to be identical with the starting material (ir). The hexane solution was concentrated to 10 ml., filtered and the solvent was removed. The oily residue upon treatment with ethanol gave colorless needles (160 mg.) m.p. 153-157°, which was recrystallized from ethanol and had m.p. 158-161° (130 mg.); ir (potassium bromide, cm^{-1}); 1739, 1660, 1617, 1250, 1035; nmr: 0.83 (3H,s), 1.36 (3H,t), 2.05 (3H,s), 4.4 (2H,q), 4.47 (2H,s), 4.4-4.9 (1H,b), 6.6 (1H,s), 7.08 (1H,s); uv: 236sh, 268, 278.5, 301 mμ (log ε 4.41, 4.10, 4.03, 3.94).

Anal. Calcd. for $C_{24}H_{31}NO_4$: C, 72.51; H, 7.86; N, 3.52. Found: C, 72.24; H, 8.05; N, 3.50.

2′,4′-Dihydro-17β-acetoxyestra-1,3,5(10)-trieno[3,2-*b*]-1′,4′-oxazine-3′-thione (XI).

(i) A refluxing solution of the lactam X (1.1 g.) in pyridine (40 ml.) was treated with phosphorus pentasulfide (1.0 g.), added in small portions, and the mixture was refluxed for 2.5 hours. The pyridine was removed under reduced pressure. The residue was decomposed with ice-water (30 ml.) and extracted with chloroform (100 ml.). The chloroform extract was washed with water, dried and evaporated. The solution of the residue in chloroform-methanol was treated with charcoal and concentrated when a solid (0.83 g.) was obtained which crystallized from methanol as yellow needles (0.58 g.) m.p. 251-253° dec. The product was found to be identical (ir) with the thioamide prepared below.

(ii) Conversion of IX to XI.

A solution of IX (0.4 g.) in dry pyridine (10 ml.) was refluxed with phosphorus pentasulfide (0.5 g.) for 1.5 hours. The reaction mixture was freed from pyridine, treated with water (30 ml.) and extracted with chloroform (30 ml.). The chloroform extract was worked-up as above. The residue upon treatment with a little methanol gave a brown solid (0.3 g.) m.p. 245-248° dec. which crystallized from methanol (charcoal) as yellow needles (0.21 g.) m.p. 256-257°; ir (cm^{-1}): 3400, 3200, 1724, 1266, 1115; nmr: 0.83 (3H,s), 2.07 (3H,s), 4.82 (2H,s), 4.5-4.9 (1H,b), 6.7 (1H,s), 6.9 (1H,s); uv: 257, 263, 306sh, 330 mμ (log ε 4.07, 4.07, 4.03, 4.22).

Anal. Calcd. for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.62; H, 7.13; N, 3.37.

3′-(Thiomethyl)-17β-acetoxyestra-1,3,5(10)-trieno[3,2-*b*]-2′H-1′,4′-oxazine (XII).

A solution of the thioamide XI (1.4 g.) in dry acetone (100 ml.) was treated with powdered potassium hydroxide (0.2 g.) and methyliodide (0.6 g.) and the mixture was refluxed for 3 hours. The solution was filtered and the solvent was removed. The residue was treated with ice-water (50 ml.) and extracted with chloroform (100 ml.). The chloroform solution was washed with water, dried and evaporated. The residue crystallized from methanol as pale yellow needles (1.4 g.), m.p. 169-171°; ir (cm^{-1}): 1724, 1620, 1582, 1250, 1015; nmr: 0.83 (3H,s), 2.08 (3H,s), 2.55 (3H,s), 4.38 (2H,s), 4.55-5.0 (1H,b), 6.61 (1H,s), 7.22 (1H,s); uv: 225, 245.5, 249, 287, 300, 318 mμ (log ε 4.17, 4.27, 4.24, 4.08, 4.08, 3.99).

Anal. Calcd. for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.5. Found: C, 68.85; H, 7.36; N, 3.36.

2′,4′-Dihydro-17β-hydroxyestra-1,3,5(10)-trieno[3,4-*b*]-1′,4′-oxazin-3′-one (XXI).

To a suspension of the ketolactam VI (17 g.) in methanol (500 ml.) at 50° was added sodium borohydride (12 g.) in small portions. The resulting solution was left at room temperature overnight, concentrated to 200 ml., diluted with water (1 liter) and acidified with glacial acetic acid when a colorless solid (15.2 g.) was obtained. A part of this solid (1.5 g.) was dissolved in chloroform and filtered through silica gel (30 g.) and eluted with a mixture of chloroform-methanol (5%) (400 ml.). The eluate crystallized from acetone (charcoal) as colorless needles (1.32 g.), m.p. 272-275° dec.; ir (potassium bromide, cm^{-1}: 3600, 3540, 3220, 3160, 1700, 1230, 1050; nmr ($DMSO^{d-6}$): 0.76 (3H,s), 4.5 (3H,m), 6.75 (2H,q); uv: 258, 292 mμ (log ε 3.77, 3.47).

Anal. Calcd. for $C_{20}H_{25}NO_3$: C, 73.36; H, 7.70; N, 4.28. Found: C, 73.36; H, 7.74; N, 4.05.

2′,4′-Dihydro-17β-acetoxy-1,3,5(10)-trieno[3,4-*b*]-1′,4′-oxazin-3′-one (XXII).

A solution of the 17-hydroxy compound XXI (4.45 g.) in pyridine (40 ml.) and acetic anhydride (30 ml.) was left at room temperature overnight. The reaction mixture was decomposed with ice-water and the precipitated solid was washed with water, dried and dissolved in chloroform. The solution was filtered through alumina (25 g.) and eluted with chloroform (800 ml.) when a solid (3.9 g.) m.p. 210-220° dec., was obtained. A part of

this solid (0.2 g.) was crystallized from methanol (charcoal) as colorless needles (0.17 g.) m.p. 228-230°; ir (cm^{-1}): 3420, 3240, 1730sh, 1700, 1250, 1035; nmr: 0.82 (3H,s), 2.08 (3H,s), 4.58 (2H,s), 4.6-5.0 (1H,b), 6.92 (2H,q); uv: 257, 292 mμ (log ε 3.84, 3.52).

Anal. Calcd. for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79. Found: C, 71.71; H, 7.59; N, 3.73.

2′,4′-Dihydro-17β-acetoxyestra-1,3,5(10)-trieno[3,4-*b*]-1′,4′-oxazine-3′-thione (XXIII).

Phosphorous pentasulfide (1.4 g.) was added to a refluxing solution of the lactam (XXII) (2 g.) in pyridine (50 ml.) and the refluxing continued for 5 hours. The pyridine was removed under reduced pressure. The residue was treated with water (50 ml.). The chloroform solution was washed with water, dried and the solution was added to a dry column of silica gel (20 g.). The column was eluted with ethylacetate when a yellow solid was obtained which was crystallized from chloroform-acetone (charcoal) when yellow needles (1.55 g.), m.p. 230-233° were obtained. The analytical sample had m.p. 232-235° dec.; ir (cm^{-1}): 3400, 1730, 1510, 1495, 1255, 1025; nmr: 0.82 (3H, s), 2.05 (3H, s), 4.8 (2H, s), 4.5-4.9 (1H, m), 6.91 (2H, q); uv: 229sh, 251.5 259, 306sh, 322 mμ (log ε, 3.95, 3.97, 4.08, 4.19).

Anal. Calcd. for $C_{22}H_{27}NO_3S$: C, 68.54; H, 7.06; N, 3.63. Found: C, 68.77; H, 7.01; N, 3.65.

3′-(Thiomethyl)-17β-acetoxyestra-1,3,5(10)-trieno[3,4-*b*]-2′*H*-1′,4′-oxazine (XXIV).

This was prepared from the thioamide XXIII in 84% yield following essentially the method of preparation of XII. The product crystallized from dichloromethane-methanol as yellow needles, m.p. 163-164°; ir (cm^{-1}): 1730, 1600, 1570, 1255, 1030; nmr: 0.83 (3H,s), 2.08 (3H,s), 2.55 (3H,s), 4.42 (2H,s), 4.6-5.0 (1H,b), 6.91 (2H,q); uv: 222, 240, 246, 291, 324sh mμ (log ε 4.17, 4.18, 4.15, 4.08, 3.79).

Anal. Calcd. for $C_{23}H_{29}NO_3S$: C, 69.14; H, 7.32; N, 3.51. Found: C, 69.17; H, 7.38; N, 3.32.

3′,4′-Dihydro-17β-hydroxyestra-1,3,5(10)-trieno[3,2-*b*]-2′*H*-1′,4′-oxazine (XXXII).

(i) From (IX).

A solution of IX (0.6 g.) in THF (30 ml.) was added to a slurry of LAH (1 g.) in THF (100 ml.) and the mixture was refluxed for 6 hours, cooled and decomposed with ethyl acetate. The THF solution was filtered and the residue was washed with hot THF. The combined THF solutions were freed from solvent and the brown oily residue was chromatographed on alumina (20 g.). Elution with benzene-ether (15%) (100 ml.) gave a colorless oil (0.33 g.) which crystallized from ether: hexane (charcoal) as colorless needles (110 mg.), m.p. 150-152° ir (cm^{-1}): 3620, 3420, 1625, 1590, 1265, 1030, 1020; nmr: 0.76 (3H,s), 3.35 (2H,m), 3.38 (2H,t), 3.5-3.75 (1H,b), 6.51 (1H,s), 6.55 (1H,s); uv: 244, 301.5 mμ (log ε 3.96, 3.63).

Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.63; H, 8.68; N, 4.46. Found: C, 76.23; H, 8.99; N, 4.23.

(ii) From (V).

A solution of the ketone V (1.3 g.) in THF (30 ml.) was added to a slurry of LAH (0.6 g.) in THF (150 ml.) and the mixture was refluxed for 6 hours, then decomposed with water. The THF solultion was filtered and the residue was washed with hot ether. The combined organic solutions were dried and concentrated. The yellow oil (1.2 g.) was filtered through alumina (40 g.) and eluted with ether followed by chloroform when an oil (1.1 g.) was obtained which crystallized from ether:hexane (charcoal) as colorless needles (0.81 g.) m.p. 152.5-153.5°, found identical with the material prepared above by mixed m.p. and ir comparison.

2′,4′-Dihydro-4′-[2-(diethylamino)ethyl]-17β-acetoxyestra-1,3,5-(10)-trieno[3,2-*b*]-1′,4′-oxazin-3′-one (XXXIII).

A suspension of the lactam X (2.5 g.) in DMF (50 ml.) was added to a slurry of sodium hydride (0.4 g. 53% mineral oil suspension) in DMF (50 ml.) and the mixture was stirred in a nitrogen-atmosphere for 2 hours, cooled in ice-bath and treated with a solution of diethylaminoethyl chloride (1.2 g.) in ether (50 ml.). The mixture was stirred at room temperature for a further 2 hours and refluxed for 1 hour, then acidified with glacial acetic acid and diluted with water (400 ml.). The aqueous solution was neutralized with solid sodium carbonate and extracted with dichloromethane which was washed with water, dried and concentrated to a brown oil (3.4 g.). The oil was chromatographed on alumina (40 g.) and eluted with benzene (200 ml.) followed by benzene:ether-1:1 (200 ml.). The combined oily eluates (2.9 g.) were found homogenous by tlc. A part of this oil in ether solution was treated with 2-propanol-hydrochloric acid and the solid hydrochloride crystallized from methanol:acetone:ether mixture as colorless needles, m.p. 226-228° dec.; ir (potassium bromide, cm^{-1}): 2720, 2450, 1740sh, 1726, 1697, 1250, 1245, 1030; nmr (perdeuteriomethanol): 0.87 (3H,s), 1.37 (8H,t), 2.03 (3H,s), 6.73 (1H,s), 7.07 (1H,s); uv: 255, 294 mμ (log ε 3.68, 3.69).

Anal. Calcd. for $C_{28}H_{41}ClN_2O_4$: C, 66.58; H, 8.18; N, 5.55. Found: C, 66.63; H, 8.46; N, 5.49.

2′,4′-Dihydro-4′-[2-(diisopropylamino)ethyl]-17β-acetoxyestra-1,3,5(10)-trieno[3,2-*b*]-1′,4′-oxazin-3′-one (XXXIV).

N-Alkylation of the lactam X with 2-diisopropylaminoethyl chloride was carried out as above. The *N*-alkylated lactam, obtained as an oil (87% yield) was converted to the hydrochloride which crystallized from acetone:ether as colorless needles, m.p. 158-162°; ir (potassium bromide, cm^{-1}): 2700-2400, 1735, 1695, 1250, 1035; nmr (perdeuteriomethanol): 0.85 (3H,s), 1.48 (12H,d), 2.03 (3H,s), 4.57 (2H,s), 6.73 (1H,s), 7.07 (1H,s); uv: 257, 295 mμ (log ε 3.73, 3.75).

Anal. Calcd. for $C_{30}H_{45}ClN_2O_4$: C, 67.58; H, 8.51; N, 5.25. Found: C, 67.50; H, 8.54; N, 5.04.

3′,4′-Dihydro-4′-[2-(Diethylamino)ethyl]-17β-hydroxyestra-1,3,5-(10)-trieno[3,2-*b*]-2′*H*-1′,4′-oxazine (XXXV).

A solution of the oily lactam XXXIII (2.6 g.) in THF (100 ml.) was added to a slurry of LAH (1 g.) in THF (100 ml.). The mixture was refluxed for 20 hours and then decomposed with water. The THF solution was filtered and the solid residue was washed with hot chloroform. The combined organic solutions were dried and evaporated when an oil (2.2 g.) was obtained which was filtered through alumina (40 g.) and eluted with chloroform (300 ml.) and then with ethyl acetate (300 ml.). The combined solids obtained upon evaporation of the solvents crystallized from ether:pentane as colorless plates (1.8 g.), m.p. 141.5-142.5°; ir (cm^{-1}): 3600, 1610, 1520, 1245, 1060; nmr: 0.76 (3H,s), 1.05 (6H,t), 2.60 (8H,q), 3.33 (4H,m), 3.5-3.8 (1H,b), 4.23 (2H,t), 6.51 (1H,s), 6.65 (1H,s); uv: 255, 310 mμ (log ε 3.82, 3.68).

Anal. Calcd. for $C_{26}H_{40}N_2O_2$: C, 75.68; H, 9.77; N, 6.79. Found: C, 75.69; H, 10.07; N, 6.64.

3′,4′-Dihydro-4′-[2-(diisopropylamino)ethyl]-17β-hydroxyestra-1,3,5(10)-trieno[3,2-*b*]-2′*H*-1′,4′-oxazine (XXXVI).

A solution of the lactam XXXIV (2.6 g.) in THF was added to a slurry of LAH (2 g.) in THF (150 ml.) and the mixture was refluxed for 7.5 hours. The reaction mixture was worked-up as above when the base XXXVI was obtained as an unstable oil (1.8 g.). An ether solution of the oil was treated with 2-propanol-hydrochloric acid to afford a vary unstable semi-solid hydrochloride which was repeatedly crystallized from acetone-ether to give monohydrochloride salt as colorless needles (0.5 g.), the product forms a foam at 137-139° and melts indefinitely at 180-200°; ir (potassium bromide, cm^{-1}): 3400, 2700-2500, 1620, 1580, 1520, 1250, 1220, 1060; nmr ($DMSO^{d-6}$): 0.7 (3H,s), 6.4 (1H,s), 6.6 (1H,s); uv: 253, 306 mμ (log ε 3.74, 3.60).

Anal. Calcd. for $C_{28}H_{45}ClN_2O_2 \cdot ½ H_2O$: C, 69.19; H, 9.50; N, 5.76. Found: C, 69.18; H, 9.50; N, 5.62.

3′,4′-Dihydro-17β-hydroxyestra-1,3,5(10)-trieno[3,4-*b*]-2′*H*-1′,4′-oxazine (XXXVII).

A suspension of the amide (VI) (3 g.) in THF (100 ml.) was added to a slurry of LAH (3 g.) in THF (200 ml.). The mixture was refluxed for 16 hours and then decomposed with water. The THF solution was filtered and the residue was washed with hot dichloromethane. The combined organic solutions were dried and evaporated to give an oil (2.3 g.) which yielded a solid (1.6 g.), m.p. 151-159° upon trituration wtih methanol. This solid on further crystallization from acetone:ether formed colorless plates (1.21 g.), m.p. 186-188°; ir (cm^{-1}): 3610, 3415, 1625, 1600, 1230, 1050, 1035; nmr: 0.78 (3H,s); 3.45 (2H,t), 3.58-4.0 (1H,b), 4.21 (2H,t), 6.70 (2H,s); uv: 245sh, 294 mμ (log ε 3.67, 3.47).

Anal. Calcd. for $C_{20}H_{27}NO_2$: C, 76.64; H, 8.68; N, 4.47. Found: C, 76.57; H, 8.76; N, 4.28.

N-Alkylation of XXII.

A mixture of the lactam XXII (3 g.) and sodium hydride (0.5 g., 53% mineral oil suspension) in DMF (100 ml.) was stirred and refluxed in a nitrogen atmosphere for 1 hour and then treated with diethylaminoethyl chloride (1.2 g.) and the refluxing continued for 1 hour. The reaction mixture, after cooling, was acidified with glacial acetic acid and diluted with water (400 ml.). The aqueous solution was filtered, extracted with dichloromethane and then basified (potassium carbonate) and extracted with chloroform (300 ml.). The chloroform solution was worked-up in the usual way when an oil (0.5 g.) was obtained which was extracted with hexane. Evaporation of the hexane solution left an oil (0.28 g.) which on treatment with 2-propanol-hydrochloric acid gave the hydrochloride. The hydrochloride crystallized from methanol:ether as colorless needles, m.p. 178-180° with shrinking at 175°. Ir (potassium bromide, cm^{-1}): 3700-3500, 2600-2400, 1760; nmr (perdeuteriomethanol): 0.76 (s), 0.83 (s), 2.0 (s), 4.36 (s), 4.45 (s), 7.02 (q); uv: 250, 290 mμ (log ε 3.73, 3.33).

Anal. Calcd. for $C_{28}H_{41}ClN_2O_4$-$C_{26}H_{39}ClN_2O_3$: C, 67.01; H, 8.27; N, 5.79. Found: C, 66.61; H, 8.39; N, 5.72.

General Procedure for the Preparation of the Amidines XIV-XX and XXV-XXXI.

The methyl thioimidates XII and XXIV were heated in benzene (5-10 ml.) with the appropriate amines (1-1.3 mol. equivalent) in presence of trimethylamine hydrochloride (catalytic amount). The completion of the reaction was checked by tlc. The product was isolated either by direct crystallization after removal of benzene or by crystallization after chromatographic purification. The reaction conditions are given in Table II and the spectral data are recorded in Table III.

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(2) Steroids with heteroatoms in the cyclopentenophenanthrene skeleton and those with additional heterocyclic ring built on the steroid nucleus have both been frequently referred to as heterocyclic steroids. To avoid confusion, we propose that the former class of steroids be named as heterocyclic steroids and the latter as steroidal heterocycles.

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