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SYNTHESIS OF NEW HETEROCYCLIC DERIVATIVES OF ESTRADIOL[1]

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Abstract—The preparation of the steroidal chromone (**4**), chromanone (**5a**), methylbenzoxazole (**6**), and methylbenzisoxazole (**7**), from the 2-acetyl steroid (**2a**) and its oxime (**2d**), is reported.

Chromone (**4**) is shown to react with hydrazine hydrate and hydroxylamine hydrochloride to provide respectively the 3'-phenylpyrazole (**10a**) and a mixture of the 5'-phenylisoxazole (**11a**) and the isomeric 3'-phenylisoxazole (**12a**).

Résumé—On rapporte la synthèse de noveaux stéroïdes hétérocycliques, à partir soit de l'acétyl-2-oestradiol (**2a**), soit de l'oxime correspondante (**2d**). Les dérivés suivants sont décrits: la chromone (**4**), la chromanone (**5a**), ainsi que les méthyl-benzoxazole (**6**) et méthyl-benzisoxazole (**7**) stéroïdiques.

La réaction de l'hydrate d'hydrazine sur le stéroïde γ-pyronique (**4**) conduit, par ouverture de l'hétérocycle, au dérivé pyrazolique (**10a**). De surcroît, le chlorhydrate d'hydroxylamine réagit sur la chromanone (**4**), par un processus similaire, pour donner un mélange du stéroïde phényl-5'-isoxazolique (**11a**) et de son isomère phényl-3'-isoxazolique (**12a**).

On discute les mécanismes de réaction, ainsi que les propriétés spectrales des nouveaux produits obtenus, en les comparant à celles de composés molèles, préparés à cet effet.

HETEROCYCLIC steroids may be divided into two groups. The first one includes compounds in which the hetero-atom is part of the cyclopentanoperhydrophenanthrene system. These substances are usually prepared by total synthesis. In the second group, an heterocycle is attached to the intact tetracyclic steroid nucleus.

Albeit numerous steroidal derivatives of the latter group have been prepared,[2] so far little attention has been paid to substitution of the aromatic A ring of estradiol (**1a**) with heterocyclic systems.[3] In this work, we wish to report the synthesis of new heterocyclic analogues of estradiol and discuss their physical properties.

Since there was no previous mention of synthesis of steroidal chromones and chromanones in the chemical literature, we focused our attention on the preparation of estradiol-[3.2*b*]-γ-pyrone (**4**) and its dihydro-derivative (**5a**).

A possible route from estradiol (**1a**) to the chromone (**4**) implied formation of the ether (**1b**), followed by hydrolysis to the acid (**1f**), ring closure, and dehydrogenation. Reaction of estradiol (**1a**) with acrylonitrile in presence of Triton B[4] afforded the nitrile ether (**1b**) identified as its acetate (**1c**) (see Experimental). Acid hydrolysis of the nitrile (**1b**) followed by reaction with hydrochloric acid in methanol solution provided the ester (**1d**), besides the 17-methyl ether (**1e**). Alkaline hydrolysis of the ester (**1d**) afforded in

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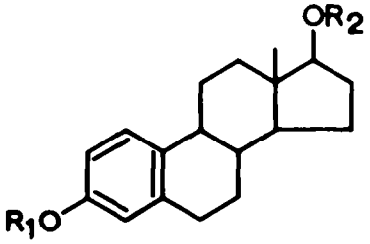
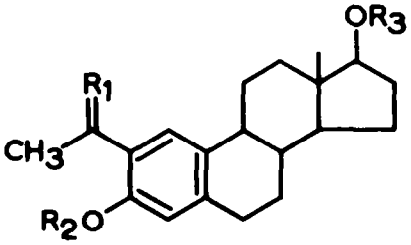
low yield the free acid (**1f**), the main compound being estradiol (**1a**), presumably by degradation of (**1d**) through a retro-Michael reaction.[5]

A more promising route to the chromone (**4**) was then investigated, using the 2-acetyl-steroid (**2a**)[6] obtained by reaction of estradiol (**1a**) with acetyl chloride. Structure **2a** was supported by its physical properties, in particular its NMR spectrum which indicated that the newly introduced acetyl group was located at position 2 and not at C-4 (Table 1).

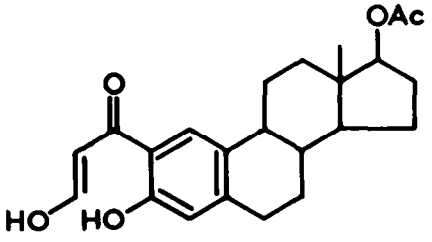
When the acetyl derivative **2a** was reacted with ethyl formate in presence of sodium or sodium hydride,[7] the unstable hydroxymethylene derivative **3** was formed. Reaction of **3** with acid afforded the steroidal chromone (**4**), characterized by its NMR spectrum



1a: $R_1 = R_2 = H$
b: $R_1 = CH_2CH_2CN; R_2 = H$
c: $R_1 = CH_2CH_2CN; R_2 = Ac$
d: $R_1 = CH_2CH_2CO_2CH_3; R_2 = H$
e: $R_1 = CH_2CH_2CO_2CH_3; R_2 = CH_3$
f: $R_1 = CH_2CH_2CO_2H; R_2 = H$



2a: $R_1 = O; R_2 = H; R_3 = Ac$
b: $R_1 = O; R_2 = R_3 = H$
c: $R_1 = O; R_2 = R_3 = Ac$
d: $R_1 = N\text{-}OH; R_2 = H; R_3 = Ac$



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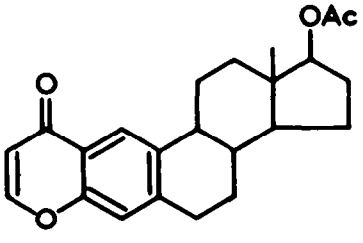

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showing a pair of doublets at 6·28 and 7·81 ppm (Table 1), attributed to the olefinic protons in α and β positions with respect to the new carbonyl grouping. Catalytic hydrogenation (Pt) of chromone (**4**) provided the chromanone (**5a**), whose oxime (**5b**) was prepared. The NMR spectrum of the chromanone (**5a**) presents triplets corresponding respectively to the protons at C-2′ and C-3′, at 2·78 and 4·51 ppm (Table 1).

The chemical shifts of the aromatic protons at positions 1 and 4 in these new heterocyclic steroids reflect both the inductive effect and the magnetic anisotropic deshielding due to the functional groups (double bond, carbonyl, etc.) of the heterocycle.

Treatment of the acetyl steroid (**2a**) with hydroxylamine gave the oxime (**2d**). On the one hand, when **2d** was reacted with benzenesulfonyl chloride or p-toluenesulfonyl chloride in pyridine,[8] the 2′-methylbenzoxazole (**6**) was formed. On the other hand, reaction of **2d** with benzenesulfonyl chloride in dilute potassium hydroxide[8] furnished the 3′-methylbenzisoxazole (**7**) (no reaction occurred when *p*-toluenesulfonyl chloride was used).

TABLE 1.

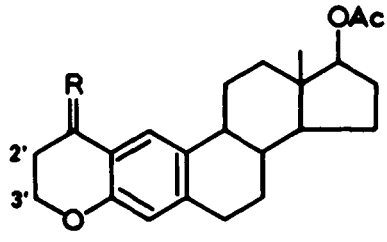
Compounds	NMR Properties in ppm
2a	7·60 (1-H); 6·71 (4-H); 2·61 (Ac)
2b	7·60 (1-H); 6·68 (4-H); 2·56 (Ac)
2c	7·75 (1-H); 6·81 (4-H); 2·50 (Ac)
2d	7·31 (1-H); 6·58 (4-H); 2·52 (2'-Me); 11·26 (3-OH); 11·35 (oxime-OH),[a]
4	8·08 (1-H); 7·14 (4-H); 6·28 (2'-H, d, J = 6 Hz); 7·81 (3'-H, d, J = 6 Hz)
5a	7·81 (1-H); 6·70 (4-H); 2·78 (2'-H, t, J = 6·5 Hz); 4·51 (3'-H, t, J = 6·5 Hz)
5b	7·77 (1-H); 6·64 (4-H); 2·96 (2'-H, t, J = 6 Hz); 4·21 (3'-H, t, J = 6 Hz)
6	7·53 (1-H); 7·13 (4-H); 2·55 (2'-Me)
7	7·50 (1-H); 7·23 (4-H); 2·53 (3'-Me)
8	6·75–7·73 (4 aromatic H); 2·55 (2-Me),[b]
9	6·62–7·72 (4 aromatic H); 2·51 (3-Me),[b]
10a	7·48 (1-H); 6·75 (4-H); 6·69 (C-4'-H, d, J = 2 Hz); 7·58 (C-5'-H, d, J = 2 Hz); 9·50 (NH and OH)
10b	7·56 (1-H); 6·59 (4-H); 6·83 (C-4'-H, d, J = 2·5 Hz); 7·81 (C-5'-H, d, J = 2·5 Hz),[a]
11a	8·1 (1-H); 7·03 (4-H); 7·30 (4'-H, d, J = 2 Hz); 8·66 (C-3'-H, d, J = 2 Hz),[c]
11b	7·80 (1-H); 6·91 (4-H); 6·45 (C-4'-H, d, J = 2 Hz); 8·28 (C-3'-H, d, J = 2 Hz)
12a	8·0 (1-H); 7·05 (4-H); 7·40 (C-4'-H, d, J = 2 Hz); 8·83 (C-5'-H, d, J = 2 Hz),[c]
12b	7·68 (1-H); 6·92 (4-H); 6·59 (C-4'-H, d, J = 2 Hz); 8·45 (C-5'-H, d, J = 2 Hz)
13	7·30–7·47 (3 aromatic H); 7·62–7·82 (2 aromatic H); 8·15 (C-3-H, d, J = 1·5 Hz); 6·42 (C-4-H, d, J = 1·5 Hz),[b]
14	7·28–7·43 (3 aromatic H); 7·65–7·85 (2 aromatic H); 6·54 (C-4 H, d, J = 1·5 Hz); 8·34 (C-5-H, d, J = 1·5 Hz)[b]

[a] In DMSO soln.
[b] 1 M soln. in CCl_4.
[c] In d_5-pyridine soln.

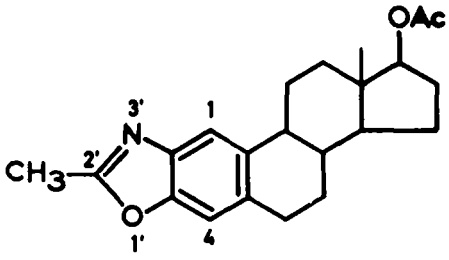
The structures assigned to compounds **6** and **7** are derived from the mechanistic pathways outlined in Chart I (see below). Whilst the IR properties of benzoxazole have been commented upon,[9] comparison of the spectra of the isomers (**6** and **7**) did not allow one to reach any satisfactory conclusion. Conversely, examination of the UV and NMR data of these substances gave valuable information, when compared with the properties of model compounds, such as 2-methylbenzoxazole (**8**) and 3-methylbenzisoxazole (**9**).

Whereas 2-methylbenzoxazole (**8**) was easily prepared by the method of Theilacker,[10] in our hands the technique reported by Lindemann *et al.*[11] for the preparation of 3-methylbenzisoxazole (**9**) lead to a 1 : 1 mixture of isomeric **8** and **9**.[12, 13] These isomers could be separated by preparative GLC. The UV properties of compounds **6** to **9** listed in Table 2 indicate that the spectrum of steroid **6** is more similar to that of the bicyclic compound **8** than its isomer **9**. Moreover, the absorption pattern of **7** is in better agreement with that of **9** than **8**. The small bathochromic and hyperchromic shifts observed in the case of the steroidal isomers **6** and **7**, compared with the model compounds **8** and **9** may be attributed to inductive and/or conformational effects induced by the polycyclic steroidal skeleton.[14]

Various authors have attempted to correlate the chemical shifts[15] of the protons in some aromatic substances with the electronic densities[16] at the corresponding positions.



5a, R = O
b, R = N-OH



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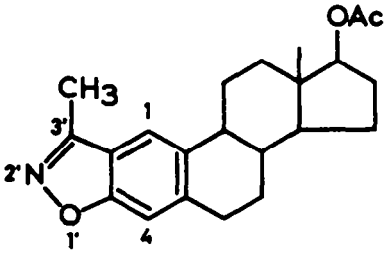

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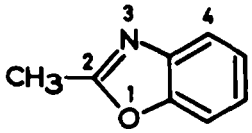

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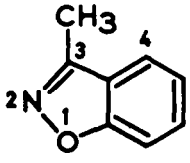

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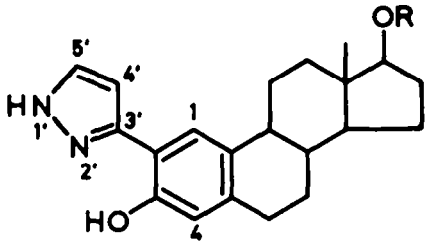


10 a, R = Ac
b, R = H

Thus, we compared the quantum mechanical data available for the molecules of benzoxazole (**8**) and benzisoxazole (**9**), with the experimental chemical shift observed for the methyl group in compounds **8** and **9**. The NMR spectra of compounds **8**[17] and **9** were obtained in carbon tetrachloride solution at 1 M concentration. The methyl resonance signals appear at 2·55 and 2·51 ppm respectively (Table 1). Hence, the available information does not allow correlation of the chemical shifts with the calculated data for electronic densities in the benzoxazole (**8**) and benzisoxazole (**9**).[15, 16]

Table 1 also reports the Me signal of the isomeric steroids (**6** and **7**). The Me signal of **6** appears at lower field than that of **7**. Worth noting is the fact that the electronic density data calculated by quantum mechanics for position 4 in benzoxazole (**8**) and benzisoxa-

TABLE 2.

Compounds	UV properties λ_{max} (nm); log ε
2a	218 (4·37); 266 (4·18); 337 (3·65)
2b	217 (4·33); 266 (4·15); 338 (3·61)
2c	216 (4·38); 256 (4·06); 290 (3·23)
2d	260 (4·11); 316 (3·67)
4	225 (4·36); 230 (4·32); 244 (4·14); 252 (4·11); 270 (3·87); 310 (3·86)
5a	218 (4·36); 262 (4·11); 336 (3·62)
5b	264 (4·07)
6	240 (4·05); 274 (3·70); 279 (3·83); 284 (3·81); 289 (3·82)
7	243 (4·00); 249 (4·04); 255 (3·96); 296 (3·64)
8	232 (4·04); 263 (3·48); 270 (3·67); 277 (3·70)
9	235 (3·89); 243 (3·83); 285 (3·42); 330 (2·85)
10a	217 (4·39); 253 (4·21); 263 (4·25); 304 (3·85); 311 (3·85)
10b	214 (4·42); 254 (4·19); 262 (4·22); 302 (3·86); 310 (3·86)
11a	226 (4·28); 266 (4·30); 276 (4·21); 316 (4·02)
11b	207 (4·27); 219 (4·30); 266 (4·29)
12a	221 (4·28); 258 (4·00); 308 (3·74)
12b	210 (4·43); 248 (4·12); 282 (3·36)
13	263 (4·20)
14	240 (4·15)

zole (**9**) [position 1 in the steroidal isomers **6** and **7**], are also in disagreement with the experimental chemical shift observed for this proton (Table 1). The chemical shifts of the aromatic protons in steroids **6** and **7**, indicate a deshielding effect on the protons at C-1 and C-4, exercised by the oxazole and isoxazole ring in these steroids. The shift is roughly the same in compounds **6** and **7** and is comparable with that observed in the γ-pyrone (**4**).[18]

In addition, the proposed structures shown in formula **6** and **7** are also in agreement with the results obtained by Blatt *et al.*[12] in other series.

From the reaction mechanism view point, the formation of isomers **6** and **7** can be rationalized as indicated in Chart I. In the weakly basic pyridine medium, the benzenesulfonate ester (**A**) of the oxime (**2d**), suffers a Beckmann rearrangement (**A**)→(**B**), before attack by the phenolic hydroxyl at C-3, to give **6**.[19]

In a strongly alkaline medium (KOH), the C-3 phenoxide anion (**C**) displaces the benzenesulfonate to afford the methylbenzisoxazole (**7**), without rearrangement. For steric reasons, the *anti* configuration of the OH group *viz.* the steroid nucleus in oxime (**2d**) is to be expected. Thus, if the above mechanisms are correct, the stereochemistry of oxime (**2d**) is automatically established, since both mechanisms (**2d**)→(**A**)→(**B**)→(**6**) and (**2d**)→(**A**)→(**C**)→(**7**) imply the configuration of the oxime to be *anti*, as in formula **2d**.[20] Furthermore, in the reaction mechanism (**2d**)→(**6**), the aromatic ring migrated, instead of the Me, also indicating this group to be in position *anti* with regard to the oxime.[21] Finally, in the reaction mechanism (**2d**)→(**7**), the benzenesulfonate group must be displaced by the phenoxide anion at C-3 in a *trans* fashion as is usually the case in nucleophilic substitution reactions.[19]

Chromones are known to react with hydrazine hydrate and hydroxylamine hydrochloride to provide rearranged compounds.[22-25] Treatment of the steroidal chromone (**4**) with hydrazine hydrate in ethanol solution afforded 3,17β-dihydroxy-2-(3′-pyrazolyl)-

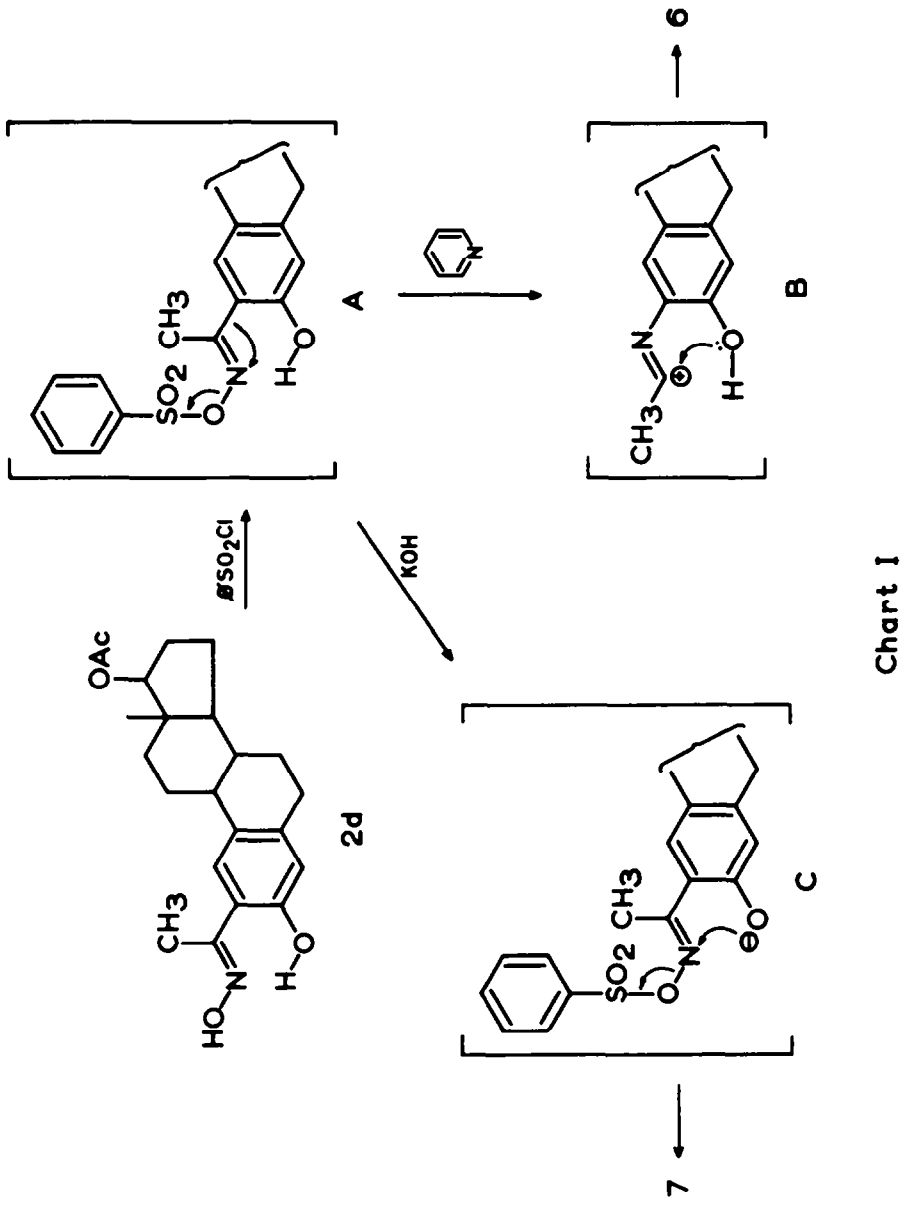


Chart I

estra-1,3,5(10)-trien 17-acetate (**10a**), whose NMR spectrum is characterized by doublets at 6·69 and 7·58 ppm ($J = 2$ Hz), corresponding to the pyrazole protons[26] at C-4′ and C-5′, (Table 1). The corresponding diol (**10b**) was obtained if an excess of water was present in the reaction medium. The pyrazole (**10a**) is presumably formed from chromone (**4**) through a reaction mechanism (**4**)→(**D**)→(**E**)→(**F**)→(**G**)→(**10a**) shown in Chart II.

The reaction of hydroxylamine with chromones has been little studied.[22] The first authors[23] thought that the products were the isomeric oximes. Later, during a study on flavones the investigators,[24] proposed an isoxazole structure. More recently, some reports appeared on the reaction of hydroxylamine with various types of chromones;[25] however, without providing convincing evidence to support the porposed structures.

In previous works,[24, 25] it is inferred that it is the 3-arylisoxazole structure which is obtained by treatment of a chromone with hydroxylamine, without apparent reason for disregarding the alternative isomeric 5-arylisoxazole. Chart II shows that a 3-arylisoxazole would result from initial attack by the oxygen atom of hydroxylamine on the γ-pyrone ring. However, taking into consideration the normal behaviour of ambident nucleophilic reagents,[27] an initial attack by the nitrogen atom should be favoured to give a 5-arylisoxazole. Furthermore, it is of interest to note that there is apparently no report on the isolation of both 3-arylisoxazole and 5-arylisoxazole isomers from the reaction of a chromone with hydroxylamine.

We wish to present evidence here that treatment of chromone (**4**) with hydroxylamine hydrochloride in pyridine solution leads to a mixture of isomeric isoxazoles (**11a** and **12a**), separated by fractional crystallization. The isoxazole (**11a**) was isolated in moderate yield. Its diacetate (**11b**) was prepared under usual acetylation conditions. The mother liquors of **11a** gave the isomeric isoxazole (**12a**), easily converted into its diacetate (**12b**).

Since comparison of neither the UV, nor the NMR properties of isomers **11a** and **12a** with those reported in the literature[28, 29] led to a definite proof of the structure, 3-phenylisoxazole (**14**) and 5-phenylisoxazole (**13**) were prepared as model compounds. 3-Phenylisoxazole (**14**) was obtained by a technique previously described,[30] but modified according to a recent report[31] on nitrile oxides (Experimental). 5-Phenylisoxazole was prepared according to the excellent method of Woodward *et al.*[32]

The relevant NMR data of compounds **11a** to **14** are listed in Table 1. It is worth mentioning that the chemical shifts of the protons vicinal to the heteroatoms in **13** and **14** are almost identical with those reported by Doorenbos *et al.*[29] The major discrepancies are found in the chemical shifts of the resonance signals of the protons at C-4. These signals appear at lower field in **13** and **14** than in the previously described steroids.[29] This can be attributed to a negative inductive effect of the aromatic ring, which due to its close location to these positions deshields them more than the others, and/or to a ring current effect.

The NMR of the 3′-arylisoxazole (**12b**) presents a pair of doublets at 6·59 and 8·45 ppm attributed to the protons on the heterocycle, in reasonable agreement with the data found for the bicyclic derivative **14** (Table 1). Similarly, the NMR properties of steroid **11b**, are reminiscent of those of the bicyclic analogue **13**.

Worth mentioning is the fact that also in this case the quantum mechanical calculations did not allow correlation of experimental chemical shifts of the protons of the heterocycle with the electron density data.[16]

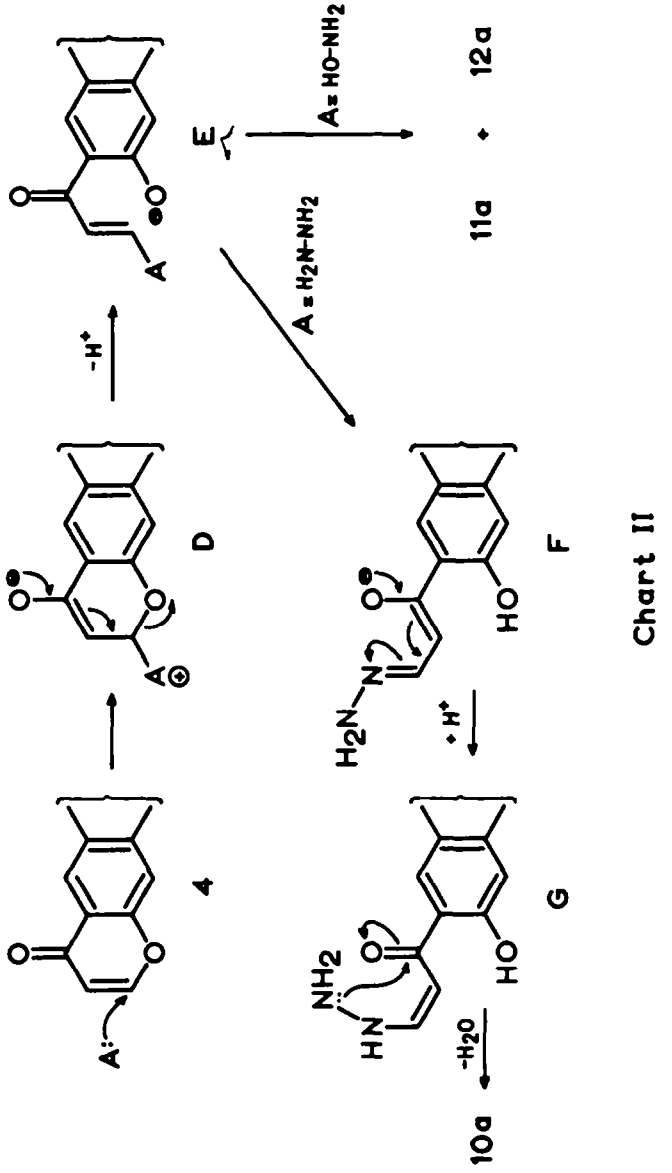
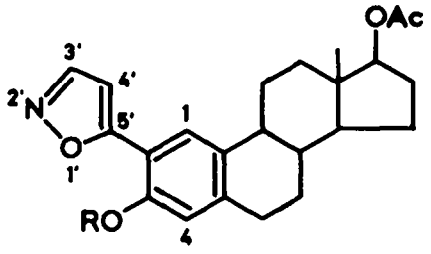
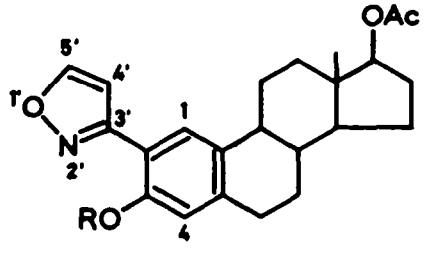


Chart II

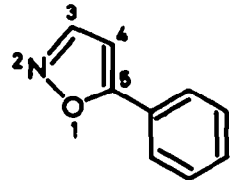
The foregoing discussion of the reaction mechanisms and spectroscopic properties of steroids **6**, **7**, **11a**, **b**, and **12a**, **b** by comparison with those of model compounds **8**, **9**, **13**, and **14**, has the feature of providing reasonable support for the proposed structures.



11a, R = H
b, R = Ac



12a, R = H
b, R = Ac



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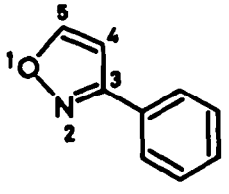

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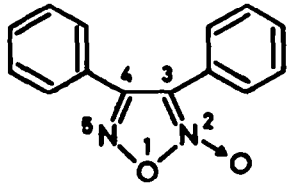

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EXPERIMENTAL

Microanalyses were done by Dr. A. Bernhardt, Mülheim, Germany. M.ps were determined with a Meltemp and Kofler apparatus and are uncorrected. Specific rotations were taken between 16 and 22° with a 1 dm tube at Na D line. IR spectra were taken with a Perkin–Elmer, Model 21, NaCl prism. UV absorption spectra were obtained in 95% EtOH with a Beckman Model DU spectrophotometer. Unless stated otherwise, NMR spectra were recorded with a Varian A-60 or H-100 spectrometer, using 5–8% w/v soln of substance in $CDCl_3$ containing TMS as an internal reference. Resonance frequencies are quoted in ppm downfield from the TMS reference and are accurate to ±0·01 ppm. Coupling constants, *J*, expressed in hertz Hz) are accurate to ±1 Hz; d refers to a doublet, t = triplet, q = quartet, m = multiplet.

3-(2′-*Cyanoethoxy*)-*estra*-1,3,5(10)-*trien*-17β-*ol* (**1b**)

To 500 mg **1a** in 10 ml dioxan, 5 ml acrylonitrile, 1 ml water, and 4 drops of 30% Triton B were added. The mixture was allowed to reflux for 2 hr. It was then concentrated to half its volume under reduced pressure. The resulting soln was poured into water, washed with 10% NaOH aq, with water, and extracted with EtOAc. The organic layer was washed with water and dried over Na_2SO_4, filtered, and evaporated to dryness *in vacuo*. The residue (350 mg) was crystallized from acetone–hexane to afford the analytical sample of **1b** as prisms, m.p. 154–155°, $[\alpha]_D$ −36°; λ_{max} 279, 287 nm (log ε 3·23, 3·20); $\nu_{max}^{CHCl_3}$ 3580, 2250, 1610, 1580 cm^{-1}. (Found: C, 77·68; H, 8·37; O, 10·01; N, 4·47. $C_{21}H_{27}O_2N$ requires: C, 77·50; H, 8·36; O, 9·83; N, 4·30%). The **1b** is most conveniently purified through its 17-acetate **1e**).

Acetylation of **1b** *to its* 17β-*acetate* (**1e**)

A soln of **1b** (100 mg) in 3 ml dry pyridine and 2 ml Ac_2O was heated on the steam-bath for 2 hr. After cooling, the mixture was poured into iced-water, and the organic compound isolated by usual procedure. The crystalline material (95 mg) was recrystallized from $CHCl_3$–MeOH to give the pure sample of **1e** as long needles, m.p. 137–138°, $[\alpha]_D$ −4°; λ_{max} 279, 287 nm (log ε 3·24, 3·20); $\nu_{max}^{CHCl_3}$ 2250, 1730, 1610, 1570, 1250 cm^{-1}; NMR 0·81 (18-H), 1·99 (17-OAc), 2·68 (t, J = 6·5 Hz, CH_2—CH), superposed on above mentioned resonance (3-benzylic H), 4·08 (t, J = 6·5 Hz, O—CH_2), 4·68 (broad, 17α-H), 6·53, 7·08 ppm (3 aromatic H). (Found: C, 75·18; H, 8·04; O, 13·22; N, 3·83. $C_{23}H_{29}O_3N$ requires: C, 75·17; H, 7·95; O, 13·06; N, 3·81%).

3-(2′-*Carbomethoxy-ethoxy*)-*estra*-1,3,5(10)-*trien*-17β-*ol* (**1d**)

To 3 g of **1e** dissolved in 60 ml glacial AcOH 60 ml conc HCl were added, and the mixture was heated under reflux for 16 hr. The mixture was cooled and concentrated *in vacuo* to ¼ of its volume. Water was added and the product was extracted with EtOAc. The organic layer was washed several times with $NaHCO_3$. This alkaline soln was treated with 20% HCl soln and extracted with EtOAc. These extracts were washed with a saturated NaCl–water soln until neutral. After distillation of the solvent under reduced pressure, the residue was treated with 4 ml anhydrous pyridine and 3 ml Ac_2O at room temp for 48 hr. After extraction the crude acetoxy-acid was dissolved in 20 ml 5% HCl–MeOH soln (2 ml AcCl in 20 ml MeOH).[33] The mixture was allowed to stand overnight at room temp and was then refluxed for 1 hr. The crude reaction product (2 g) was purified by chromatography over florisil. Elution with benzene–hexane (7 : 3) afforded 600 mg of the 17-ether (**1e**). Recrystallization from MeOH furnished the analytical sample of **1e**, m.p. 92–93°, $[\alpha]_D$ + 45°; λ_{max} 281, 289 nm (log ε 3·20, 3·17); $\nu_{max}^{CHCl_3}$ 3400 (solvated H_2O), 1730, 1605 cm^{-1}; NMR 0·76 (18-H), 2·76 (t, J = 6·5 Hz, $OCH_2\underline{CH_2}$—CO_2CH_3), 4·20 (t, J = 6·5 Hz, $O\underline{CH_2}CH_2CO_2CH_3$), 3·68 (17-$OCH_3$), 3·71 ($CO_2CH_3$), 6·61, 6·76, 7·10 (3 aromatic H). (Found: C, 70·37; H, 8·88. $C_{23}H_{32}O_4,H_2O$ requires: C, 70·74; H, 8·78%).

Further elution with benzene–hexane (9 : 1) provided 450 mg of the 17-alcohol (**1d**). Recrystallization from hexane gave the pure sample as small needles, m.p. 100–101°, $[\alpha]_D$ + 50°; λ_{max} 280, 288 nm (log ε 3·29, 3·27); $\nu_{max}^{CHCl_3}$ 3560, 1730, 1600 cm^{-1}; NMR 0·79 (18-H), 2·78 (t, J = 6·5 Hz, $OCH_2\underline{CH_2}CO_2CH_3$), 4·25 (t, J = 605 Hz, $OCH_2CH_2CO_2CH_3$), 3·73 (CO_2CH_3), 6·65, 6·78, 7·15 and 7·29 ppm (3 aromatic H). (Found: C, 73·48; H, 8·40; O, 18·40. $C_{22}H_{30}O_4$ requires: C, 73·71; H, 8·44; O, 17·85%).

3-(2′-*Carboxy-ethoxy*)-*estra*-1,3,5(10)-*trien*-17β-*ol* (**1f**)

A soln of 150 mg of methyl ester (**1d**) in 20 ml EtOH and 2 ml water, containing 650 mg $NaHCO_3$ was heated under reflux for 3 hr. As soon as the reflux started, a strong odor of methyl acrylate [formed by retro-Michael on **1d**] could be detected. The soln was cooled, the solvent distilled under reduced pressure; water and EtOAc were added to the residue which was washed with $NaHCO_3$ aq. The organic phase was washed, dried, and the solvent removed *in vacuo*. The crude product was recrystallized from MeOH, affording 75 mg of **1a** (m.p. 173–174°), shown to be identical with an authentic sample by usual criteria (mixed m.p., IR, and TLC).

The alkaline extracts were acidified with 10% HCl aq and extracted with EtOAc. After usual isolation procedure, 50 mg of **1f** was obtained. Recrystallization from MeOH afforded the analytical sample as needles, m.p. 203–204°, $[\alpha]_D$ + 70°; λ_{max} 281, 289 nm (log ε 3·28, 3·25); ν_{max}^{KBr} 3450, 3400–2600, 1725, 1610, 1550 cm^{-1}. (Found: C, 73·16; H, 8·25; O, 18·51. $C_{21}H_{28}O_4$ requires: C, 73·22; H, 8·19; O, 18·58%).

2-*Acetyl*-3,17β-*dihydroxy-estra*-1,3,5(10)-*trien*-17-*acetate* (**2a**)

To a mixture of dry chlorobenzene (100 ml), acetyl chloride (4 ml), and anhyd $AlCl_3$ (10 g), cooled to 0°, 5 g of **1a** was added, with vigorous stirring over a period of 3 hr. The mixture was left overnight at room temp. The orange-red colored complex which formed was decomposed with a dil HCl aq. Extraction with EtOAc, washing with water, and drying over Na_2SO_4 provided, after filtration and distillation of the solvents, an oily residue. Addition of MeOH furnished crystals (from 2·2 g to 3·5 g, depending on the experiment) of **2a**[6] as nice prisms, m.p. 195–197°, $[\alpha]_D$ + 51°; λ_{max} 218, 266, 337 nm (log ε 4·37, 4·18, 3·65); ν_{max}^{KBr} 3400, 1730, 1650, 1620, 1250 cm^{-1}; NMR 0·86 (18-H), 2·08 (17-OAc), 2·61 (—CO—CH_3), 2·84 (benzylic-H), 6·71, 7·60 (2 aromatic H), 12·0 ppm (chelated OH, disappears with D_2O). (Found: C, 74·17; H, 8·08; O, 18·08. $C_{22}H_{28}O_4$ requires: C, 74·13; H, 7·92; O, 17·96%).

The residual oily product obtained after separation of **2a** was submitted to steam distillation which

eliminated *p*-chloro acetophenone formed during the reaction. After extraction with ethyl acetate by usual procedure, a mixture of two main components was obtained. On the one hand, this mixture was dissolved in dry pyridine (5 ml) and acetylated with Ac_2O (4 ml) one night at room temp. After extraction and crystallization from methanol, 2·6 g of the pure sample of **2e** was obtained, m.p. 148–150°, $[\alpha]_D$ − 103°; λ_{max} 216, 256, 290 nm (log ε 4.38, 4·06, 3·23); ν_{max}^{KBr} 1780, 1725, 1680, 1610 cm^{-1}; NMR 0·83 (18-H), 2·05 (17-OAc), 2·31 (3-OAc), 2·50 (—CO—CH_3), 6·81 (4-H), 7·75 ppm (1-H). (Found: C, 71·99; H, 7·54. $C_{24}H_{31}O_5$ requires: C, 72·59; H, 7·58%).

On the other hand, this mixture was separated by TLC using benzene–EtOAc (4 : 1) as eluent, affording **2a** and **2b**, as needles, after several crystallizations from MeOH, m.p. 195–196°, $[\alpha]_D$ + 98°; λ_{max} 217, 266, 338 nm (log ε 4·33, 4·15, 3·61); ν_{max}^{KBr} 3420, 1630, 1610, 1570 cm^{-1}; NMR 0·76 (18-H), 1·45 (OH-17, disappears with D_2O), 2·56 (—CO—CH_3), 6·68 (4-H), 7·60 (1-H), 12·01 ppm (chelated OH, disappears with D_2O). (Found: C, 75·86; H, 8·24. $C_{20}H_{25}O_3$ requires: C, 76·39; H, 8·30%).

Compound **2e** can be hydrolized selectively into **2a** using a K_2CO_3—H_2O—MeOH solution.

Oxime (**2d**) *of* 2-*acetyl*-3,17β-*dihydroxy-estra*-1,3,5(10)-*trien*-17-*acetate*

A mixture of 200 mg (**2a**), NH_2OH,HCl (200 mg), EtOH (10 ml), and pyridine (5 ml) was gently heated under reflux for 4 hr. After cooling and solvent removal, water was added. Extraction with EtOAc, followed by washing with dil HCl, water, and drying, furnished 200 mg of crystalline residue. Recrystallization from chloroform–methanol gave the analytical sample of **2d** as light needles, m.p. 249–250°, $[\alpha]_D$ + 74°; λ_{max} 260, 316 nm (log ε 4·11, 3·67); $\nu_{max}^{CHCl_3}$ 3500, 3350 (OH associate), 1735, 1630, 1575, 1250 cm^{-1}; NMR (d_6DMSO), 0·78 (18-H), 2·0 (17-OAc), 2·22 (vinylic CH_3), 6·58 (C-4 aromatic H), 7·31 (C-1 aromatic H), ~ 11·30 ppm (3-OH and N—OH, exchanged with D_2O). (Found: C, 71·31; H, 7·96; O, 17·36; N, 3·86. $C_{22}H_{29}O_4N$ requires: C, 71·13; H, 7·87; O, 17·23; N, 3·77%).

[3,2b]-γ-*Pyrone-estra*-1,3,5(10)-*trien*-17β-*ol-acetate* (**4**)

To a suspension of 10 g powdered Na and 50 ml ethyl formate (redistilled over P_2O_5), cooled to 0°, a soln of 4 g (**2a**) in 200 ml dry ethyl formate was added dropwise, with stirring. The mixture kept at 0°, was stirred for 14 hr. The excess of Na was carefully destroyed with MeOH. Then water and AcOH were added. The excess of ethyl formate was removed by vacuum distillation. The residue was extracted with EtOAc, washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give the amorphous derivative **3** (violet color with $FeCl_3$). It was not purified but immediately dissolved in 50 ml glacial AcOH; concentrated HCl (15 ml) was added, and the mixture was allowed to reflux for 45 min. After cooling, part of the AcOH was eliminated *in vacuo*, the soln was then diluted with water and extracted with EtOAc. After usual work-up and decoloration with Norite A, followed by preparative TLC and recrystallization from MeOH, 50% of pure **4** was obtained as prisms, m.p. 210–211°, $[\alpha]_D$ + 99°; λ_{max} 225, 230, 244, 252, 270, 310 nm (log ε 4·36, 4·32, 4·14, 4·11, 3·87, 3·86); ν_{max}^{KBr} 1730, 1650, 1625, 1595, 1250 cm^{-1}; NMR 0·84 (18-H), 2·07 (17-OAc), 2·98 (benzylic H), 6·28 (d, J = 6 Hz, vinylic H of γ-pyrone), 7·14 and 8·08 (aromatic H), 7·81 (d, J = 6 Hz, vinylic H of pyrone). (Found: C, 75·28; H, 7·22; O, 17·60. $C_{23}H_{26}O_4$ requires: C, 75·38; H, 7·15; C, 17·47%).

5′,6′-*Dihydro*-[3,2b]-γ-*pyrone-estra*-1,3,5(10)-*trien*-17β-*ol-acetate* (**5a**)

To a prehydrogenated suspension of 66 mg PtO_2 in glacial AcOH, 250 mg chromone (**4**) was added. The mixture was shaken in H_2 atmosphere until one equivalent of H had been taken. The catalyst was filtered off and the soln was concentrated *in vacuo*. After concentration to half its volume, water was added, and the mixture extracted with EtOAc. The organic layer was washed with $NaHCO_3$ aq and then with water until neutral. After drying over Na_2SO_4, filtration, and evaporation to dryness, the analytical sample of the dihydro **5a** (200 mg) was obtained by crystallization from acetone–hexane: silky plates, m.p. 157–159°; $[\alpha]_D$ + 195°; λ_{max} 218, 262, 336 nm (log ε 4·36, 4·11, 3·62); ν_{max}^{KBr} 1730, 1680, 1615, 1555, 1250 cm^{-1}; NMR 0·84 (18-H), 2·08 (17-OAc), 2·78 (t, J = 6·5 Hz, CO—$\underline{CH_2}$—), 4·51 (t, J = 6·5 Hz, O—$\underline{CH_2}$—), 6·70, 7·81 (aromatic H). (Found: C, 75·15; H, 7·78; O, 17·51. $C_{23}H_{28}O_4$ requires: C, 74.97; H, 7·66; O, 17·37%).

Oxime (**5b**) *of* 5′,6′-*dihydro*-[3,2b]-γ-*pyrone-estra*-1,3,5(10)-*trien*-17β-*ol-acetate*

To 130 mg of **5a**, 150 mg hydroxylamine hydrochloride, 5 ml EtOH, and 5 ml pyridine were added. This soln was allowed to reflux for 3 hr. Water was added, and extraction with EtOAc, followed by washing with dil HCl, and water, providing 120 mg of crystalline **5b**. Recrystallization from $CHCl_3$–MeOH gave the

pure sample as long needles, m.p. 250–252° (dec), $[\alpha]_D$ + 88°; λ_{max} 264 nm (log ε 4·07); $\nu_{max}^{CHCl_3}$ 3550, 3400 (associated OH), 1725, 1630, 1600, 1250 cm^{-1}; NMR 0·83 (18-H), 2·07 (17-OAc), 2·96 (t, J=6 Hz, $\underline{CH_2}$—C=N—), 4·21 (t, J=6 Hz, $\underline{CH_2}$—O—), ~4·75 (17α-H), 6·64 (C-4 aromatic H), 7·77 (C-1 aromatic H), 8·11 ppm (N—OH, disappears with D_2O). (Found: C, 72·21; H, 7·80; O, 16·81; N, 3·59. $C_{23}H_{29}O_4N$ requires: C, 72·03; H, 7·62; O, 16·69; N, 3·65%).

[3,2d]-2′-*Methyloxazole-estra*-1,3,5(10)-*trien*-17β-*ol acetate* (**6**)

(a) *Benzenesulfonyl chloride technique.* The oxime **2d** (150 mg) was dissolved in 4 ml anhyd pyridine and 0·5 ml benzenesulfonyl chloride was added dropwise, with vigorous stirring. The soln, originally colorless, became intensely red and was allowed to stay 1 hr at room temp. Water was added and extraction with EtOAc was followed by washing with 5% HCl, water, drying, and evaporation. After decoloration with Norite A, 100 mg of crystalline **6** was obtained. Recrystallization from MeOH provided the analytical sample as prisms, m.p. 159–160°, $[\alpha]_D$ −40°; λ_{max} 240, 274, 279, 284, 289 nm (log ε 4·05, 3·70, 3·83, 3·81, 3·82); $\nu_{max}^{CHCl_3}$ 1730, 1610, 1580, 1245 cm^{-1}; NMR 0·85 (18-H), 2·09 (17-OAc), 2·55 (oxazole methyl), 2·98 (benzylic H), 7·13 and 7·53 ppm (aromatic H). (Found: C, 74·83; H, 7·66; O, 13·71; N, 4·03. $C_{22}H_{27}O_3N$ requires: C, 74·75; H, 7·70; O, 13·58; N, 3·96%).

(b) p-*Toluenesulfonyl chloride technique.* The oxime **2d** (300 mg) was dissolved in 8 ml anhyd pyridine, and 1·5 g *p*-toluenesulfonyl chloride was added in small portions. The original colorless soln became orange-red and was allowed to stay 1 hr at room temp. After the same treatment as above, 184 mg of crystalline **6** was obtained. Recrystallization from MeOH provided the pure sample of **6** as prisms, m.p. 159–160°, $[\alpha]_D$ −40°.

[3,2d]-3′-*Methylisoxazole-estra*-1,3,5(10)-*trien*-17β-*ol acetate* (**7**)

A suspension of 150 mg of **2d** in 5 ml of a 20% KOH–water soln was vigorously shaken for 3 min, then 0·6 ml of benzenesulfonyl chloride was added. The mixture was shaken for 2 additional hr, diluted with water, and extracted with EtOAc, then washed, dried, and evaporated. The residue was crystallized from MeOH (90 mg), thus affording the pure sample of **7**, m.p. 181–182°, $[\alpha]_D$ + 98°; λ_{max} 243, 249, 255, 296 nm (log ε 4·00, 4·04, 3·96, 3·64); $\nu_{max}^{CHCl_3}$ 1725, 1610, 1590, 1245 cm^{-1}; NMR 0·76 (18-H), 2·0 (17-OAc), 2·53 (isoxazole methyl), 2·95 (benzylic H), 7·23 and 7·53 ppm (aromatic H). (Found: C, 74·58; H, 7·68; O, 13·73; N, 3·77. $C_{22}H_{27}O_3N$ requires: C, 74·75; H, 7·70; O, 13·58; N, 3·96%).

2-*Methylbenzoxazole* (**8**). Prepared by the method of Theilacker:[10] e_{573} 188–192°; λ_{max} 232, 263, 270, 277 nm (log ε 4·04, 3·48, 3·67, 3·70); ν_{max}^{neat} 1616, 1575 cm^{-1}; NMR (CCl_4), 2·55 (2-CH_3), 6·75–7·73 ppm (4 aromatic H).

3-*Methylbenzisoxazole* (**9**). The technique of Lindemann *et al.*[11] led to a 1 : 1 mixture of **8** and **9** (shown by NMR and GLC). These isomers were separated by GLC with a Varian Aerograph 705, using 610 × 1 cm aluminum column filled with 15% SE-30 on chromosorb W; the column temp was 281°; the retention times were: 2-methylbenzoxazole (**8**): 9·1 min; and 3-methylbenzisoxazole (**9**): 10·2 min.

Compound **9** showed, e_{10} 95°; λ_{max} 235, 243, 285, 330 nm (log ε 3·89, 3·83, 3·42, 2·85); ν_{max}^{neat} 1650, 1620, 1580 cm^{-1}; NMR (CCl_4), 2·51 (3-CH_3), 6·62–7·72 ppm (4-aromatic H).

3,17β-*Dihydroxy*-2-(3′-*pyrazolyl*)-*estra*-1,3,5(10)-*trien*-17-*acetate* (**10a**)

To 150 mg of **4** in 5 ml EtOH, 1 ml NH_2—NH_2,H_2O in 1 ml EtOH was added, and the mixture was gently refluxed for 30 min. The mixture was cooled, poured into water, and extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and concentrated *in vacuo*, affording 100 mg **10a**. The analytical sample recrystallized from acetone–hexane, gave **10a** solvated with acetone as light prisms, m.p. 260–262°, $[\alpha]_D$ + 194°; λ_{max} 217, 253, 263, 304, 311 nm (log ε 4·39, 4·21, 4·25, 3·85, 3·85); $\nu_{max}^{CHCl_3}$ 3440, 3300, 1725, 1710 (acetone), 1630, 1580, 1250 cm^{-1}; NMR 0·84 (18-H), 2·09 (17α-H), 2·19 ($\frac{1}{2}$ mole acetone), 2·82 (benzylic H), 6·69 (pyrazole H), 6·75, 7·48 (aromatic H), 7·58 (pyrazole H), 9·50 ppm (broaden signal, OH and NH, disappears with D_2O). (Found: C, 72·16; H, 7·43; O, 14·05; N, 6·38. $C_{23}H_{28}O_3N_2$, $\frac{1}{2}$ CH_3COCH_3 requires: C, 71·88; H, 7·58; O, 13·69; N, 6·84%).

3,17β-*Dihydroxy*-2-(3′-*pyrazolyl*)-*estra*-1,3,5(10)-*triene* (**10b**)

Treatment of **4** with NH_2—NH_2,H_2O, containing an excess of water, under the above conditions, afforded exclusively **10b**. Recrystallization from $CHCl_3$–MeOH gave the analtyical sample as large prisms, m.p. 297–299°, $[\alpha]_D$ + 203°; λ_{max} 214, 254, 262, 302, 310 nm (log ε 4·42, 4·19, 4·22, 3·86, 3·86); ν_{max}^{KBr} 3540 (NH), 3425–3100 cm^{-1} (OH and NH associated), 1630, 1580 cm^{-1}; NMR (d_6DMSO) 0·69 (18-H),

6·59 (C-4 aromatic H), 6·83 (C-4'—H, d, $J=2$ Hz), 7·56 (C-1 aromatic H), 7·81 ppm (C-5'—H, d, $J=2·5$ Hz). (Found: C, 74·29; H, 7·40; O, 9·88; N, 8·72. $C_{21}H_{26}O_2N_2$ requires: C, 74·52; H, 7·74; O, 9·46; N, 8·28%).

This compound **10b** was identical (mixed m.p., IR, and TLC) with a sample obtained by direct alkaline hydrolysis of the acetate **10a**.

3,17β-*Dihydroxy*-2-(5'-*isoxazolyl*)-*estra*-1,3,5(10)-*trien*-17-*acetate* (**11a**) *and* 3,17β-*dihydroxy*-2-(3'-*isoxazolyl*)-*estra*-1,3,5(10)-*trien-acetate* (**12a**) *and the* 3,17-*diacetate* (**12b**).

A mixture of 400 mg of **4**, 150 mg NH_2OH, HCl in 10 ml EtOH, and 5 ml dry pyridine was heated under reflux for 4 hr and then left at room temp overnight. The reaction mixture was concentrated under reduced pressure, water was added, and the soln extracted with EtOAc. The organic layer was washed with water, dried over Na_2SO_4, filtered, and evaporated to furnish 130 mg of **11a**. The analytical sample was obtained by several crystallizations from EtOAc, as prisms, m.p. 239–240° (dec), $[\alpha]_D$ + 75°; λ_{max} 226, 266, 276, 316 nm (log ε 4·28, 4·30, 4·21, 4·02); ν_{max}^{KBr} 3450–3350 and 3200–3150 (associated OH), 1730, 1620, 1575, 1250 cm^{-1}; NMR (d_5-pyridine) 0·85 (18-H), 2·06 (17-OAc), 7·03 (4-H), 8·1 (1-H), 7·30 and 8·66 ppm (3'-H and 4'-H, d, $J=2$ Hz). (Found: C, 72·33; H, 7·16; O, 16·64; N, 3·54. $C_{23}H_{27}O_4N$ requires: C, 72·42; H, 7·13; O, 16·78; N, 3·67%).

The mother liquors were evaporated to dryness, affording 310 mg of a mixture constituted mainly by the isomers **11a** and **12a**.

On the one hand, this mixture was heated with 3 ml Ac_2O in 5 ml pyridine one night at room temp. After usual extraction procedure, 150 mg **12b** was obtained. The analytical sample was recrystallized from $CHCl_3$–MeOH to afford white plates, m.p. 201–202°, $[\alpha]_D$ + 120°; λ_{max} 210, 248, 282 nm (log ε 4·43, 4·12, 3·36); ν_{max}^{KBr} 1770, 1730, 1610, 1550, 1250 cm^{-1}; NMR 0·85 (18-H), 2·07 (17-OAc), 2·29 (3-OAc), 2·92 (broad, benzylic H), 6·59 (d, $J=2$ Hz, isoxazole H), 6·92, 7·68 (aromatic H), 8·45 ppm (d, $J=2$ Hz, isoxazole H). (Found: C, 70·72; H, 6·91; O, 18·97; N, 3·46. $C_{25}H_{29}O_5N$ requires: C, 70·90; H, 6·90; O, 18·89; N, 3·31%). Alkaline hydrolysis (K_2CO_3—H_2O—MeOH) of **12b** gave **12a**.

On the other hand, this residue was separated by TLC using benzene–EtOAc (4:1) as eluent, affording 45 mg of **11a** and 70 mg of **12a**, as white plates from $CHCl_3$–MeOH, m.p. 225–227°, $[\alpha]_D$ + 56°; λ_{max} 221, 258, 308 nm (log 4·28, 4·00, 3·74); $\nu_{max}^{CHCl_3}$ 3500–3260 (OH assoc), 1725 (17β-OAc), 1630, 1580 cm^{-1}; NMR (d_5-pyridine) 0·81 (18-H), 2·03 (17-OAc), 5·33 (broad OH), 7·05 (4-H), 8·0 (1-H), 7·40 (d, $J=2$ Hz, 4'-H) and 8·83 ppm (d, $J=2$ Hz, 5'-H).

3,17-*Dihydroxy*-2-(5'-*isoxazolyl*)-*estra*-1,3,5(10)-*trien*-3,17 *diacetate* (**11b**)

82 mg of **11a** were treated with 3 ml Ac_2O in 5 ml dry pyridine one night at room temp. After usual extraction procedure 90 mg of **11b** were obtained as plates from $CHCl_3$–MeOH, m.p. 174–175°, $[\alpha]_D$ + 60°; λ_{max} 207, 219, 266 nm (log ε 4·27, 4·30, 4·29); ν_{max}^{KBr} 1760, 1720, 1615, 1590 cm^{-1}; NMR 0·81 (18-H), 2·03 (17-OAc), 2·33 (3-OAc), 6·45 (d, $J=2$ Hz, isoxazolyl-4'-H), 8·28 (d, $J=2$ Hz, 3'-H isoxazole), 6·91 (4-H) and 7·80 ppm (1-H). (Found: C, 70·72; H, 6·91; N, 3·24. $C_{25}H_{29}O_5N$ requires: C, 70·90; H, 6·90; N, 3·31%).

5-*Phenylisoxazole* (**13**)

Prepared by the method of Woodward *et al*;[32] λ_{max} 263 nm (log ε 4·20); ν_{max}^{neat} 1610, 1595, 1575 cm^{-1}; NMR (CCl_4) 6·42 (d, $J=1·5$ Hz, C—4-H), 8·15 (d, $J=1·5$ Hz, C—3-H), 7·30–7·47 (3 aromatic H), 7·62–7·82 ppm (2 aromatic H).

3-*Phenylisoxazole* (**14**)

(a) *Benzonitrile oxide.* In a 1l. separating funnel, 15 g benzaldoximes dissolved in 100 ml DMF was introduced. N-bormosuccinimide (22 g) dissolved in 50 ml DMF was added. To this red exothermic reaction mixture, cooled to 5°, 25 g triethylamine in 50 ml DMF was added portion-wise with vigorous shaking. The solid which formed during the addition of triethylamine dissolved by addition of iced-water (300 ml) and ether (250 ml). At the end of the addition of triethylamine, the red color changed to light yellow. The ether layer was separated, and the water phase was extracted again with ether. The organic phase was washed and used as such for the next step.

(b) 3-*Phenyl*-5-*acetoxy*-Δ^2-isoxazoline. To the ethereal soln of benzonitrile oxide, cooled to 0°, 25 ml recently distilled vinyl acetate in 50 ml ether was added portion-wise, with stirring in a period of 10 min. The mixture was left for 30 min at 0°, then filtered to separate 2·3 g of **15** (m.p. 110°). The ether soln was allowed

to stand at room temp for 3 hr, then it was dried and concentrated *in vacuo*. The residue afforded 9 g (36%) of a slightly yellow crystalline material, m.p. 86–87°.[31]

(c) 3-*Phenylisoxazole* (**14**). The previously described procedure[30] was followed to provide 89% of **14**, e_{11} 122°; λ_{max} 240 nm (log ε 4·15); ν_{max}^{neat} 1590, 1560 cm^{-1}; NMR (CCl_4) 6·54 (d, J = 1·5 Hz, C—4-H), 8·34 (d, J = 1·5 Hz, C—5-H), 7·28–7·43 (3 aromatic H), 7·65–7·85 ppm (2-aromatic H).

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