STEROIDS AND RELATED STUDIES. PART 73. STEROIDAL [3,4-c]-1',2',5'-OXADIAZOLES

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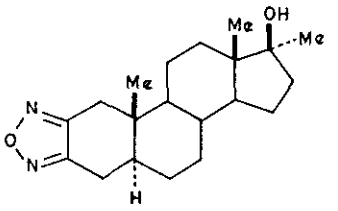
Abstract —— A procedure for the synthesis of steroidal [3,4-c]-1',2',5'-oxadiazoles has been developed. The sequence consists of converting 4-en-3-ones to 4,5-oxido-3-ones, rearrangement of the oxiranes to 4-hydroxy-4-en-3-one system, which forms the 3,4-dioxime, changing to the oxadiazole on treatment with alkali. The synthesis of 5-epimeric 5ξ-cholestano [3,4-c]-1',2',5'-oxadiazoles 5 is described. Synthesis of 17-hydroxy-17α-methyl-5ξ-androstano [3,4-c]-1',2',5'-oxadiazoles 2, first attempted by starting with methyltestosterone, has been achieved from oxymesterone 9. The 5α- (HS-805) and 5β- (HS-804) isomers have been separated. HS-805 has been found to be less active than furazabol 1 which is the respective [2,3-c]-1',2',5'-oxadiazole.

Interest has been shown in the biological activity of steroidal [2,3-c]-1',2',5'-oxadiazoles. Furazabol, chemically 17-hydroxy-17α-methyl-5α-androstano [2,3-c]-1',2',5'-oxadiazole 1,[1-3] is an anabolic steroid with relatively low androgenicity.[2,4,5] It is used clinically. Derivatives of parenterally active 17β-hydroxy-5α-androstano [2,3-c]-1',2',5'-oxadiazole with different substitutions at 17α- and 16-positions have been studied but no better compound than the parent substance was obtained.[6,7] Pregn-4-eno [2,3-c]-1',2',5'-oxadiazol-20-one was 0.2 times as active as progesterone in progestational activity.[8] As an

anti-inflammatory agent 11β,17α,21-trihydroxypregn-4-eno [2,3-c]-1',2',5'-



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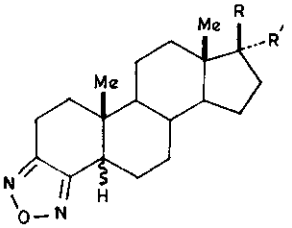
oxadiazol-20-one was found to be as active as hydrocortisone.[8]

The above cited heterocyclic steroids have the oxadiazole system fused to positions 2,3. We conceived preparing analogues with the oxadiazole system fused to the 3,4-position. After exploratory work in the cholestane and androstane series, we succeeded in preparing 17-hydroxy-17α-methyl-5ξ-androstano [3,4-c]-1',2',5'-oxadiazoles 2. A preliminary report regarding it was made earlier,[9]



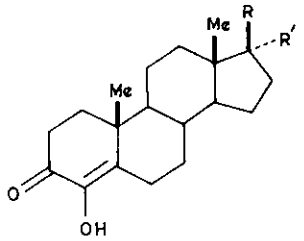
2 R=OH, R'=CH_3

5 R=C_8H_{17}, R'=H

and in this paper we describe the details.

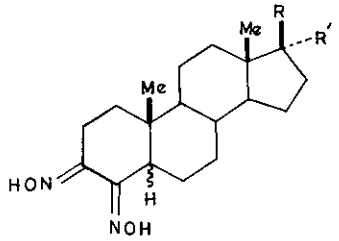
To start with, known 4β,5-oxido-5β-cholestan-3-one[10] was prepared. The NMR spectrum showed a singlet at δ 2.95, evidently for 4α-proton. On acid treatment the oxirane rearranged to 4-hydroxycholest-4-en-3-one 3.[11] It showed a singlet at δ 6.07 for 4-OH which disappeared on deuterium exchange. The enol 3 corresponding to 3,4-dione on heating with hydroxylamine-pyridine gave the dioxime 4. The latter on heating with potassium hydroxide in ethylene

glycol gave the oxadiazoles 5. On careful fractional crystallisation it was possible to separate the mixture into products A (mp 156-157°C) and B (mp



3 R=C_8H_{17}, R'=H

9 R=OH, R'=CH_3

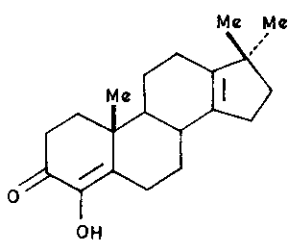


4 R=C_8H_{17}, R'=H

10 R=OH, R'=CH_3

108-109°C) in 37 and 29% yields. The former showed 18-Me and 19-Me singlets at δ 0.70 and 1.20 whereas the latter exhibited these singlets at δ 0.71 and δ 0.75. These are the two 5-epimers.

Next, the synthesis of the androstane derivative 2 was thought of. Treatment of methyltestosterone with alkaline hydrogen peroxide gave 17-hydroxy-17α-methyl-4ξ,5-oxido-5ξ-androstan-3-one[12] which was mostly the 4β,5β-isomer containing about 10% of 4α,5α-component. The area under singlets at δ 2.96 (4α-H) and 3.03 (4β-H) was in the ratio 9:1, and both together integrated for one proton. When the oxirane mixture was treated with mineral acid in acetic



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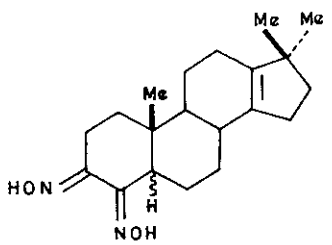

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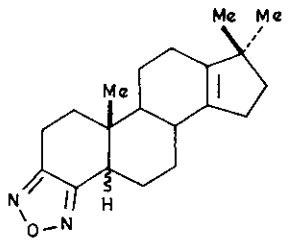
acid, not unexpectedly, there occurred Wagner-Meerwein rearrangement and the product obtained characterised as the structure 6: ultraviolet maximum at

276 nm; vibrational bands at 1390 and 1360 cm^{-1} for gem-dimethyl; and NMR signals at δ 0.97(s,6H; 17,17-(CH_3)$_2$, 1.16 (s,3H; 19-CH_3) and 6.12 (1H, disappearing on deuterium exchange; 3-OH). The rearrangement of 17β-hydroxy-17α-alkylandrostanes to give 17,17-dimethyl-13-unsaturated steroids is well documented.[13] The dioxime 7 was prepared which was converted to the oxadiazole 8 which could not



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be separated into its components.

Finally, oxymesterone 9 (kindly supplied by Farmitalia Carloerba, Milano, Italy) was treated with hydroxylamine hydrochloride in pyridine to give the dioxime 10. Refluxing of the dioxime with potassium hydroxide in ethylene glycol gave the oxadiazoles 2. By no other way but fractional crystallisation the products HS-805 (mp 174-175°C) and HS-804 (mp 216-218°C) were separated in 48 and 36% yields. HS-804 showed 18-Me and 19-Me at δ 0.85 and 1.15, and HS-805 exhibited the respective signals at δ 0.89 and 0.75.

X-ray diffraction studies[14] indicate HS-804 to be the 5β-isomer and HS-805 to be the 5α-epimer.

The Mitsubishi Chem. Ind. Research Institute examined the anabolic activities of oxadiazoles 2 HS-804 (5β) and HS-805 (5α) on castrated male Wistar strain rats. HS-805 showed anabolic activity, though the effect at 10 mg/kg s.c. was weaker than that of furazabol 1 at 1 mg/kg s.c. dose with an activity of about 1/10 of furazabol. The androgenic activity ratio of HS-805 to furazabol was about equal to anabolic activity ratio. HS-804 had no anabolic and androgenic activity.

EXPERIMENTAL

IR spectra were obtained for potassium bromide discs. NMR spectra (60 MHz) were recorded for solutions in deuteriochloroform containing tetramethylsilane as internal reference. Chloroform was used as solvent for determination of optical rotations. TLC was carried out on silica gel G (E. Merck) and plates were developed by exposure to iodine vapour. Anhydrous sodium sulphate was employed as the drying agent. The melting points reported are uncorrected.

3,4-Dioximino-5ξ-cholestane 4. — Hydroxylamine hydrochloride (0.42 g) was added to a solution of 4-hydroxycholest-4-en-3-one 3 (1.0 g) in dry pyridine (5.2 ml). The reaction mixture was heated on steam bath for 1.5 h, poured into water (300 ml), filtered, washed and dried. The residue so obtained was crystallised from methanol to yield 4 (0.5 g, 47%), mp 218-219°C (decomp.); UV (MeOH) 222 nm (log ε 3.79); IR(KBr): 3205, 1640 and 1560 cm^{-1}; $[\alpha]_D^{27}$ - 12.5° (c 0.40); Anal. Found: C, 75.22; H, 10.90; N, 6.32. Calcd. for $C_{27}H_{46}N_2O_2$: C, 75.28; H, 10.76; N, 6.50%.

5ξ-Cholestano[3,4-c]-1',2',5'-oxadiazoles 5. — A mixture of 3,4-dioximino-5ξ-cholestane 4 (1.0 g) and potassium hydroxide (0.8 g) in ethylene glycol (20 ml) was refluxed for 1 h. The reaction mixture was poured into ice-cold water (1 litre) and the precipitate was filtered, washed and dried. Dry residue was crystallised from ethanol to give the product A 5 in first crop (0.35 g, 37%), mp 156-157°C; UV (MeOH) 217 nm (log ε 3.51); IR (KBr): 2825, 1450 and 1380 cm^{-1}; $[\alpha]_D^{24}$ + 89.83 (c 1.00); δ 0.70 (3H, s) and 1.20 (3H, s); Anal. Found: N, 6.37. Calcd. for $C_{27}H_{44}N_2O$: N, 6.79%).

The mother liquor was concentrated and allowed to crystallise to afford B 5 (0.28 g, 29%), mp 108-109°C; UV(MeOH) 217 nm (log ε 3.74); IR(KBr) 2860, 1450 and 1375 cm^{-1}; $[\alpha]_D^{27}$ + 10.9° (c 0.32); δ 0.71 (3H, s) and 0.75 (3H, s); Anal. Found: C, 78.62; H, 10.89; N, 6.67. Calcd. for $C_{27}H_{44}N_2O$: C, 78.59; H, 10.75; N, 6.79%.

17,17-Dimethyl-4-hydroxy-18-norandrosta-4,13-dien-3-one 6. — 17β-Hydroxy-4ξ,5-oxido-5ξ-androstan-3-one (2.0 g) was dissolved in glacial acetic acid (40 ml) by slight warming. After cooling to room temperature, the solution was treated with concentrated sulphuric acid (2 ml) and shaken continuously for 2-3 min. The colour of the reaction mixture changed first to yellow and then to red.

The reaction mixture was kept at room temperature for 17 h with occasional shaking and then poured into ice-cold water (800 ml) and extracted with benzene (3 x 100 ml). The benzene extract was washed, dried and the solvent removed under reduced pressure. The residue obtained was crystallised from methanol to yield 6 (1.3 g, 69%), mp 125-126°C; UV(MeOH) 276 nm (log ε 4.06); IR(KBr) 3335, 1680, 1640, 1390 and 1360 cm^{-1}; $[\alpha]_D^{27}$ + 32° (c 0.38); δ 0.97 (6H, s), 1.16 (3H, s) and 6.12 (1H, disappearing on deuterium exchange); Anal. Found: C, 79.62; H, 9.36. Calcd. for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%.

17,17-Dimethyl-3,4-dioximino-18-nor-5ξ-androst-13-ene 7 . — Hydroxylamine hydrochloride (0.42 g) was added to a solution of 17,17-dimethyl-4-hydroxy-18-norandrosta-4,13-dien-3-one 6 (1.0 g) in dry pyridine (5.2 ml). The reaction mixture was heated on a steam bath for 1.5 h., poured into water (300 ml), filtered, washed and dried. The residue so obtained was crystallised from methanol to yield 7 (0.65 g, 59%), mp 232-233°C (decomp.); IR(KBr) 3145, 1635, 1560, 1390 and 1360 cm^{-1}; $[\alpha]_D^{27}$-85° (c 0.32); δ 0.78 (3H, s) and 0.96 (6H, s); Anal. Found: C, 72.69; H, 9.28; N, 8.39. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48%.

17,17-Dimethyl-18-nor-5ξ-androst-13-eno[3,4-c]-1',2',5'-oxadiazole 8 . — A suspension of 17,17-dimethyl-3,4-dioximino-18-nor-5ξ-androst-13-ene 7 (0.5 g) and potassium hydroxide (0.4 g) in ethylene glycol (10 ml) was refluxed for 2 h. The reaction mixture was poured into water (200 ml) and the precipitated material was filtered, washed and dried. The residue obtained was crystallised from methanol to yield 8 (0.31 g, 64%), mp 105-106°C; IR(KBr) 1590, 1495, 1390, 1365 and 870 cm^{-1}; $[\alpha]_D^{27}$ -42° (c 0.37); δ 0.71 (3H, s) and 0.97 (6H, s); Anal. Found: C, 76.80; H, 9.10; N, 8.86. Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97%.

17α-Methyl-3,4-dioximino-5ξ-androstan-17β-ol 10 . — 4-Hydroxy-17α-methyl-testosterone 9 (5.0 g) and hydroxylamine hydrochloride (2.0 g) in pyridine (25 ml) were heated on a steam bath for 2 h. The mixture was poured into ice-cold water and the precipitate was filtered, washed and dried. The residue was crystallised from methanol to give the product 10 (4.9 g, 84%), mp 230-232°C (decomp.); UV(MeOH) 223 nm (log ε 3.75); IR(KBr) 3175, 2860, 1605, 1525, 1385, 1170, 1080, 970 and 860 cm^{-1}; δ 0.80 (3H, s), 0.85 (3H, s) and 1.19 (3H, s);

Anal. Found: C, 68.60; H, 9.31; N, 7.90. Calcd. for $C_{20}H_{32}N_2O_3$: C, 68.93; H, 9.26; N, 8.04%.

17-Hydroxy-17α-methyl-5ξ-androstano[3,4-c]-1',2',5'-oxadiazoles 2. — A suspension of 17α-methyl-3,4-dioximino-5ξ-androstan-17β-ol 10 (2.0 g) and potassium hydroxide (1.0 g) in ethylene glycol (25 ml) was refluxed for 1 h, during which all the compound dissolved. The reaction mixture was poured into ice-cold water, and the precipitate filtered, washed and dried. The residue was crystallised from methanol. Two types of crystals appeared; one as needle shaped and other rhombic. The separation of crystals was done mechanically with the help of spatula. The needle shaped product was recrystallised from methanol to afford HS-804 2 (0.7 g, 36%), mp 216-218°C; UV(MeOH) 219 nm (log ε 3.52); IR(KBr) 3280, 2860, 1455, 1385, 1170, 1090, 1065, 935, 890, 875 and 860 cm^{-1}; $[\alpha]_D^{24}$ + 64.4° (c 1.00); δ 0.85 (3H, s), 1.15 (3H, s) and 1.18 (3H, s); Anal. Found: C, 72.92; H, 9.20; N, 8.34. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48%.

The other product was recrystallised from the same solvent to yield HS-805 2 (0.9 g, 48%), mp 174-175°C; UV(MeOH) 219 nm (log ε 3.49); IR (KBr) 3400, 2860, 1450, 1375, 1180, 1085, 950, 880 and 825 cm^{-1}; $[\alpha]_D^{24}$ -27.2° (c 1.00); δ 0.75 (3H, s), 0.89 (3H, s) and 1.24 (3H, s); Anal. Found: C, 72.61; H, 9.15; N, 8.38. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48%.

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