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2-OXASTEROIDS: A NEW CLASS OF BIOLOGICALLY ACTIVE COMPOUNDS

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THE substitution of a hetero atom for a 2-methylene group in steroid hormones should lead to products useful in the elucidation of the mechanism of biological action of these compounds. While such a replacement is not expected to change the shape of the molecule and is compatible with the presence of the highly important 4,5 double bond, it alters considerably the chemical nature of carbon 3 (for example, replacement of the 2-methylene group by oxygen converts a 3-ketone to a lactone). A transformation of this type permits the study of the influence of the chemical reactivity of carbon 3 on the biological activity of the molecule. In 1956 experiments were initiated in this laboratory towards the preparation and the evaluation of this new and interesting class of compounds.

When 1-androstene-3,17-dione (I) was treated with 4 equivalents of lead tetraacetate in 90 per cent aqueous acetic acid[1,2] overnight at room temperature, and the resulting crude secoaldehyde-acid II reduced with aqueous sodium borohydride followed by acid treatment, there was obtained in about 50-60 per cent yield 17β-hydroxy-2-oxaandrostane-3-one[3] (III),

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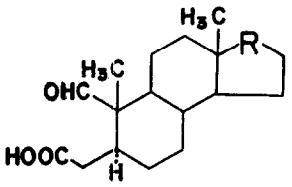
[1] R. Pappo, D.S. Allen, Jr., R.V. Lemieux and W.S. Johnson, J. Org. Chem. 21, 478 (1956).

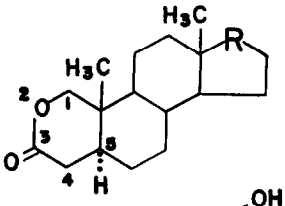
[2] R. Pappo and A. Becker, Bull. Res. Council Israel 5A, 300 (1956).

[3] Satisfactory analytical data were obtained for all the new compounds described in this communication. Rotations were determined in chloroform in about 1 per cent concentration. Ultraviolet absorption spectra were obtained in methanol and infrared absorption spectra in chloroform unless otherwise specified.



II R = C = O

VI R = C(OH)CH$_3$



III R = C(OH)H

IV R = C=O

VIII R = C(OH)CH$_3$

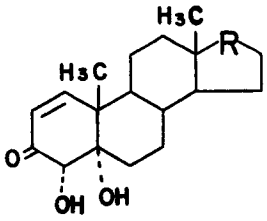
m.p. 198°-203°, λ_{max} 2.75 and 5.78 μ; $[\alpha]_D^{24}$ +1°, which on chromic acid oxidation gave the corresponding 17-ketone IV, m.p. 174°-175°, λ_{max} 5.77 μ. Similar treatment of 17β-hydroxy-17α-methyl-1-androsten-3-one[4] (V) led to the corresponding 17β-hydroxy-1-oxo-1,2-seco-A-nor-17α-methylandrostan-2-oic acid (VI), m.p. 166°-173° (dec.), λ_{max} 2.77, 2.85, 3.70, 5.80 μ; $[\alpha]_D^{25}$ -22.5°. Alternatively VI was also obtained via lead tetraacetate cleavage of 1α,2α, 17β-trihydroxy-17α-methylandrostan-3-one (VII), m.p. 180°-188° (dec.); λ_{max} 2.80, 2.89, 5.81 μ; $[\alpha]_D^{26}$ +15°, prepared by hydroxylation of V with potassium chlorate in the presence of catalytic amounts of osmium tetroxide in aqueous t-butyl alcohol. Sodium borohydride reduction of the aldehyde acid VI gave 17β-hydroxy-17α-methyl-2-oxaandrostan-3-one (VIII), m.p. 235°-238°; λ_{max} 2.87 and 5.79 μ; $[\alpha]_D^{25}$ -23°.

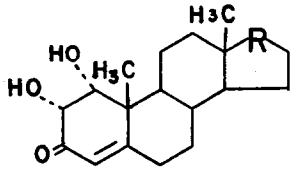
The synthesis of the analogous 4,5 unsaturated compounds proved to be considerably more difficult. When 1,4-androstadiene-3,17-dione (IX) was treated in aqueous t-butyl alcohol with potassium chlorate in the presence of a catalytic amount of osmium tetroxide, unexpectedly, the preponderant product proved to be 4α,5α-dihydroxy-1-androstene-3,17-dione[5] (X), m.p.

[4] R.E. Counsell, P.D. Klimstra and F.B. Colton, J. Org. Chem. 27, 248 (1962).

[5] The assignment of the α configuration is based on the assumption that the bulky osmium tetroxide reagent approaches the double bond from the less hindered α side.

205°-209°; λ_{max}^{MeOH} 228 mμ, ε = 9500; λ_{max} 2.80, 2.88, 5.76, 5.93 μ; $[\alpha]_D^{28}$ +151°.





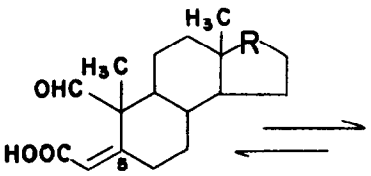
X R = C=O

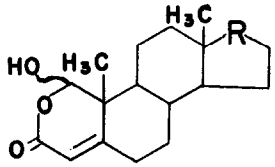
XIV R = C(OH)CH3

XI R = C=O

XV R = C(OH)CH3

Fractional crystallization of the mother liquors gave the required 1α,2α-dihydroxy-4-androstene-3,17-dione[5] (XI), m.p. 205°-209°; λ_{max} 238 mμ, ε = 13,700; λ_{max} 2.80, 2.87, 5.75, 5.95, 6.19 μ; $[\alpha]_D^{27}$ +168.5°, in about 10 per cent yield.[6] Cleavage of XI with lead tetraacetate in aqueous acetic acid at about 60° gave 1,17-dioxo-1,2-seco-A-nor-3-androsten-2-oic acid (XII), (existing mostly as the lactol form, 1-hydroxy-2-oxa-4-androstene-3,17-dione), m.p. 250°-259°; λ_{max} 226 mμ, ε = 14,000; λ_{max} 2.80, 3.00, 5.78, 5.88 and 6.12 μ; $[\alpha]_D^{27}$ +279.5°. Conventional sodium borohydride reduction





XII R = C=O

XVII R = C(OH)CH3

XIX R = C(COCH3)H

XXII R = C(COCH3)OAc

6 It is interesting to note that when the same procedure was applied to Cortisone BMD, a preponderance of the 1,2 glycol was obtained. [cf. also R. Hirschmann, G.A. Bailey, R. Walker and J.M. Chemerda, J. Amer. Chem. Soc. 81, 2822 (1959)]. It is not clear why the presence of the 11-carbonyl should cause a reversal of the ratio of isomers formed.

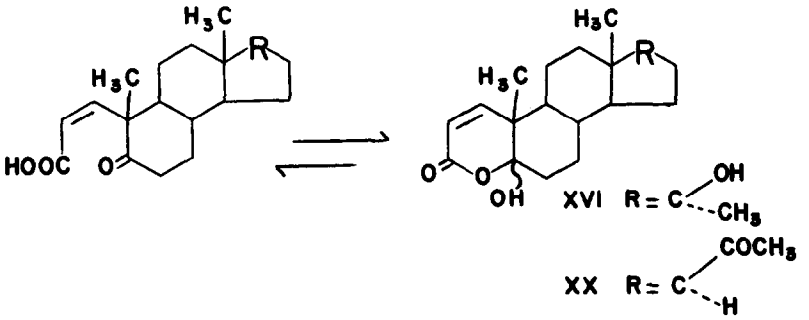
of XII with aqueous methanolic sodium borohydride in the presence of a slight excess of sodium hydroxide gave rise to a mixture containing large amounts of saturated lactonic products. A more selective reduction of the aldehyde function was effected by stirring a chloroform solution of XII with one equivalent of sodium hydroxide in the presence of an excess of sodium borohydride. It was found that the 17β-hydroxy-2-oxa-4-androsten-3-one (XIII) formed was selectively extracted from the reaction mixture by the organic solvent and therefore protected from further reduction. In this manner pure XIII was obtained, m.p. 205°-207°; λ_{max} 223.5 mμ, ε = 14,500; λ_{max} 2.76, 5.80, 5.88, 6.14 μ; $[\alpha]_D^{28}$ +173°.

Similar treatment of 17β-hydroxy-17α-methyl-1,4-androstadien-3-one gave predominantly 4α,5α,17β-trihydroxy-17α-methyl-4-androsten-3-one (XIV), m.p. 196°-199°; λ_{max} 229.5 mμ, ε = 9350; λ_{max} 2.81, 2.89, 5.93, 6.20 μ; $[\alpha]_D^{26}$ +57.5°. Fractional crystallization of the mother liquors followed by treatment with aqueous sodium bisulfite in pyridine to remove any XIV present, gave the required 1α,2α,17β-trihydroxy-17α-methyl-4-androsten-3-one (XV), m.p. 193°-195.5°; λ_{max} 239 mμ, ε = 13,300; λ_{max}^{KBr} 2.85, 3.00, 5.90, 5.96, 6.19 μ; $[\alpha]_D^{27}$ +63°.

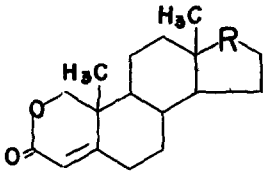
The isomers XIV and XV were separately treated with lead tetraacetate to give respectively 17β-hydroxy-3,5-seco-5-oxo-17α-methyl-A-nor-1-androsten-3-oic acid (XVI) (in equilibrium with the lactol form 5,17β-dihydroxy-17α-methyl-4-oxa-1-androsten-3-one), m.p. 227°-230°; $\lambda_{220\ m\mu}$, ε = 7500; λ_{max}^{KBr} 3.00, 3.15, 5.93 and 6.18 μ, and the lactol 1,17β-dihydroxy-17α-methyl-2-oxa-4-androsten-3-one (XVII), m.p. 250°-265°; λ_{max} 226 mμ, ε = 14,200; λ_{max}^{KBr} 2.85, 3.05, 5.85 and 6.13 μ. In comparing the properties of XVI and XVII, it was found that the latter was a considerably weaker acid than XVI. In practice the keto acid XVI could be extracted selectively from a chloroform solution of the two acids with dilute aqueous potassium or sodium carbonate solution, while it was necessary to use dilute hydroxide

solution to extract XVII. This method of separation proved to be of general application, thus affording a convenient way to isolate pure 2-oxa-Δ^4-steroids.

The lactol XVII in chloroform was reduced, as described previously, to the corresponding 17β-hydroxy-17α-methyl-2-oxa-androsten-3-one (XVIII), m.p. 230°-240° (dec.); λ_{max} 223.5 mμ, ε = 12,500; λ_{max} 2.75, 5.78, 5.85 and 6.13 μ; $[\alpha]_D^{26}$ +123°.



When the same series of reactions were applied to Δ^1-progesterone, a mixture of 1,2-dihydroxyprogesterone and 4,5-dihydroxy-1-pregnene-3,20-dione was obtained, which on treatment with lead tetraacetate gave 1-hydroxy-2-oxa-progesterone (XIX) together with 5-hydroxy-4-oxa-1-pregnene-3,20-dione (XX). This mixture was separated by partition with aqueous potassium carbonate, as described previously in the androstane series, thus affording pure XIX, m.p. 220°-223°; λ_{max} 226.5 mμ, ε = 14,300; λ_{max} 2.80, 3.00, 5.79, 5.88 and 6.12 μ; $[\alpha]_D^{26}$ +268° (0.5%), and pure XX, m.p. 203°-206°; $\lambda_{220\ m\mu}$, ε = 8300; λ_{max} 2.80, 2.97, 5.80 and 5.87 μ; $[\alpha]_D^{28}$ +275.5°. Sodium borohydride reduction of XIX in a two-phase system as described in the androstane series, followed by chromic acid oxidation of the resulting mixture of epimeric 20-hydroxy compounds, gave 2-oxaprogesterone (XXI), m.p. 168°-169°; λ_{max} 223.5 mμ, ε = 14,150; λ_{max} 5.80, 5.85 and 6.13 μ; $[\alpha]_D^{26}$ +237.5°. Starting from 17α-acetoxy-Δ^1-progesterone and employing an analogous sequence of reactions there was obtained 1-hydroxy-17α-acetoxy-



XIII R = C(OH)H

XVIII R = C(OH)CH$_3$

XXI R = C(COCH$_3$)H

XXIII R = C(COCH$_3$)OAc

2-oxa-progesterone (XXII), m.p. 285°-288° (dec.); λ_{max} 226 mμ, ε = 14,400; λ_{max} 2.75, 2.98, 5.76, 6.10 and 7.90 μ; $[\alpha]_D^{24}$ +137°. Reduction of this material with sodium borohydride in isopropanol gave 17α-acetoxy-2-oxa-progesterone (XXIII), m.p. 275°-279°; λ_{max} 223.5 mμ, ε = 14,900; λ_{max} 5.80, 5.83, 6.15 and 7.97 μ; $[\alpha]_D^{23}$ +114.5°.

Results

Preliminary results on the biological evaluation of some of the 2-oxa-steroids indicate that 2-oxa-17α-methyltestosterone (XVIII) is about as anabolic as 17α-methyltestosterone but only one-fifth as androgenic when assayed by intramuscular injection in the levator ani test.[7] Moreover, 17β-hydroxy-17α-methyl-2-oxaandrostan-3-one (VIII) proves to be more active than 17β-hydroxy-17α-methylandrostan-3-one as an anabolic agent when administered orally in the nitrogen retention test[8] but is essentially devoid of androgenic properties.[9] Clinical results, to be published elsewhere, have confirmed these biological findings, demonstrating that VIII is a potent, orally active and useful anabolic agent.

The high biological activity of 2-oxasteroids is not confined to the

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[7] E. Eisenberg and G.S. Gordon, J. Pharm. Exp. Ther. 59, 38 (1950).

[8] F.J. Saunders and V.A. Drill, Metabolism 7, 315 (1958).

[9] H.D. Lennon and F.J. Saunders, Proc. Soc. Exp. Biol. Med. In press.

androstane series. Preliminary results also indicate that 2-oxaprogesterone and 17α-acetoxy-2-oxaprogesterone are about as active as progesterone and 17α-acetoxyprogesterone, respectively, when administered by subcutaneous or buccal route to rabbits (Clauberg assay).[10]

Discussion

The results obtained in this work coupled with the recently disclosed anti-inflammatory properties of 2-oxacorticoids[11] show that as far as the anabolic, progestational and corticoid-like activities are concerned, 2-oxasteroids containing a 4,5-unsaturated 3-keto system are about equivalent to the corresponding normal steroids. However, such a biological equivalence is not compatible with the well known considerable chemical difference existing between a lactone and a ketone (differences in rates of addition and in the nature of the reaction products). These two facts could be reconciled only by assuming that the 3-carbonyl is not involved chemically in the mechanism of biological action of these hormones. This is the first time such an important observation has ever been reported.

Extension of this work to other ring-A heterocyclic steroids is in progress.

Acknowledgements - The authors are indebted to Dr. F.B. Colton for encouragement and valuable discussions.

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[10] Dr. R.L. Elton, Private communication.

[11] R. Hirschmann, N.G. Steinberg and R. Walker, Abstracts 140th Meeting of the American Chemical Society, September, 1961.