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STEROIDS AND RELATED PRODUCTS. XXVI.[1]

THE FUNCTIONALIZATION OF THE 17-METHYL GROUP OF 17α-METHYL STEROIDS. I. THE SYNTHESIS OF 12α,17[1]-EPOXY-17α-METHYLPROGESTERONE.[2]

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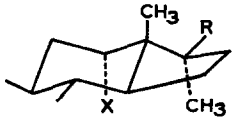
The potentiating effect of a 17α-methyl group on the progestational activity of progesterone analogues (2-6) and the observation that esters of 17α-hydroxyprogesterone exhibit marked oral progestational activity (7-10)[3], seems to make the investigation of progesterones with a functionalized 17α-methyl substituent desirable. The interest in related compounds of the corticoid series becomes apparent if one considers that a 17α-hydroxy substituent increases the glucocorticoid activity and, especially, the anti-inflammatory activity. In this paper we report the first synthesis of a hormone analogue of the progesterone-corticoid group with a functionalized 17α-methyl substituent : 12α,17[1]-epoxy-17α-methylprogesterone (III), and the synthesis of the first 17α-(hydroxymethyl) derivative of a steroid with a side chain in position 17β.

For the functionalization of the 17α-methyl substituent, we took recourse to free radical transfer reactions, taking advantage of the almost ideal stereochemical relationship between the quasi-axial 17α-methyl substituent and an axial 12α-substituent (cf. FIG. 1).



X=OH, ONO

FIG. 1

1) For paper XXV of this series see reference (1).
2) The work reported here is part of the D.Sc. thesis which will be submitted by G.J. Beaudouin to the School of Graduate Studies, Laval University.
3) Only a selection of references is given.

Methyl 3-oxo-12α-hydroxy-17α-methyl-5β-etianate (I)(3) was transformed in 97% yield to its 3-ethylenedioxy derivative (Ia), m.p. 188-188.5°, $[\alpha]_D^{22}$ +50.7°[4,5], which was treated for 17 hrs. with lead tetra-acetate in refluxing cyclohexane (11,12)[2]. This resulted in the formation (50% yield) of methyl 3-ethylenedioxy-12α,17[1]-epoxy-17α-methyl-5β-etianate (II), m.p. 148-148.5°, $[\alpha]_D^{23}$ +36.3°, ν_{max}^{KBr} 1740 cm^{-1} (ester), 1112, 1098, 1058 cm^{-1} (C-O bands); δ 0.73 (s) and 0.94 (s) (19- and 18-CH_3), 3.71 (s) (ester), 3.92 (s) (4H) (ketal), 3.75 (d) (10 cps) and 4.45 (d) (10 cps) (17α-CH_2), 4.0 (t) (12β-H)[6].

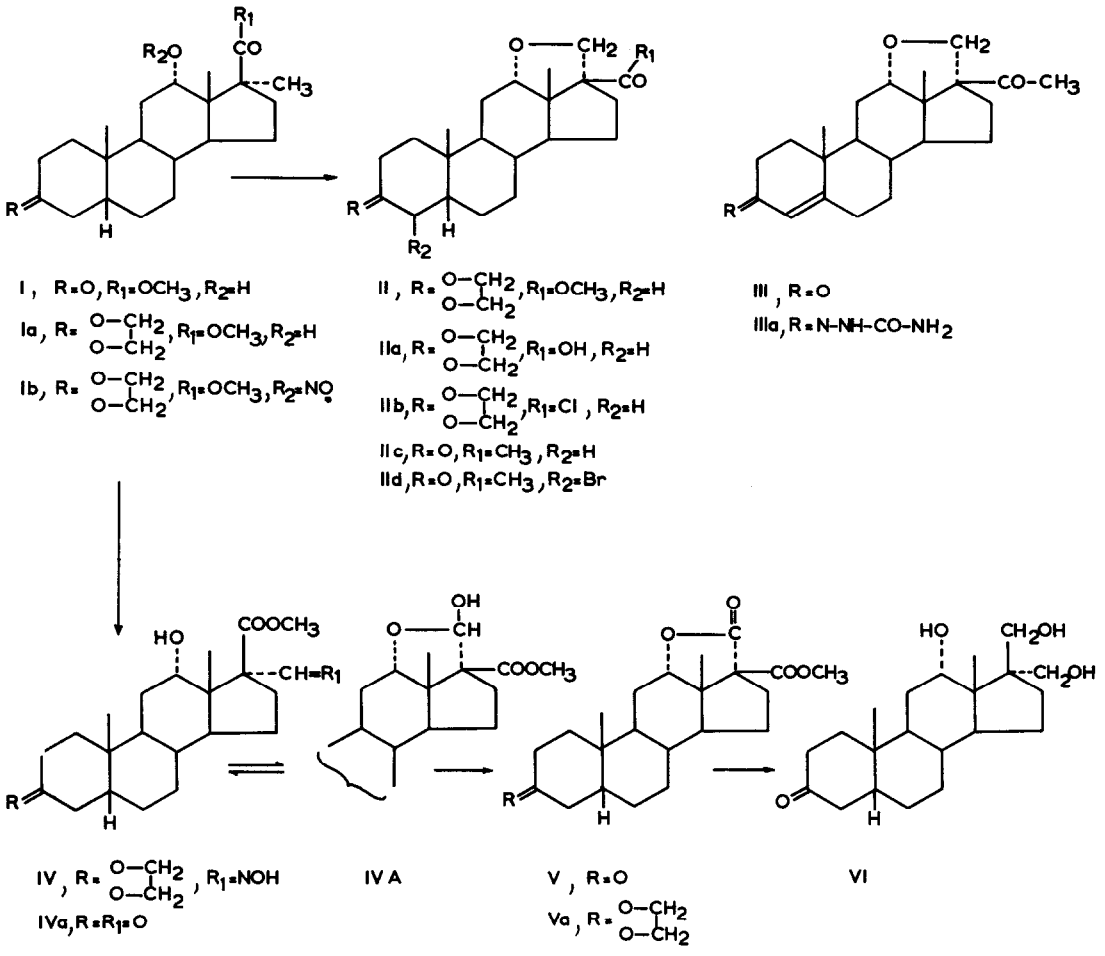
Whereas the saponification of 17-methylated etianic esters can be carried out only under very vigourous conditions (13,14)[2], that of ester II, in which the 17-methyl substituent is connected with position 12 by an ether linkage, proceeds smoothly; thus the acid ketal IIa, m.p. 302-303°, $[\alpha]_D^{22}$ +45° (dioxane), was obtained in over 90% yield by the action of a 6.5% methanolic potassium hydroxide solution at reflux temperature. The greater reactivity of the 20 position of ethers of type II as compared to classical 17-methyl steroids is also exemplified by the observation that the reaction of ester II with methyl magnesium bromide under conditions in which a 17α-methylated etio ester gives a considerable proportion of methyl ketone (15,16), leads entirely to the tertiary alcohol.

Acid IIa was transformed with oxalyl chloride (17,19) to the acid chloride IIb which was treated without purification with dimethyl cadmium to give, after hydrolysis in position 3, 12α,17[1]-epoxy-17α-methyl-5β-pregnane-3,20-dione (IIc), m.p. 208-209°, ν_{max}^{KBr} 1718 cm^{-1} (3-ketone), 1702 cm^{-1} (20-ketone), 1059 cm^{-1} (ether); δ 0.78 (s) (19-CH_3), 1.04 (s) (18-CH_3), 2.18 (s) (21-methyl-20-ketone), 4.07 (t) (2.2 cps) (12β-H), 3.78 (d) (10 cps) and 4.42 (d) (10 cps) (17α-CH_2).

The double bond in position 4 was introduced by the formation of the 4β-bromide IId, m.p. 173-175° (dec.), its treatment with semicarbazide and an exchange reaction of the semicarbazone IIIa (λ_{max}^{EtOH} 269 mμ) with pyruvic acid (20). Thus the desired 12α,17[1]-epoxy-17α-methyl-4-pregnene-3,20-dione (III), m.p. 203-204°, $[\alpha]_D^{22}$+106°,

4) Rotations were taken, if not otherwise stated, in chloroform.
5) Only significant spectral data are reported. For all new compounds isolated in the pure state, satisfactory analytical results were obtained.
6) The NMR spectra were recorded on a Varian A 60 instrument (60Mc), in deutero-chloroform, tetramethylsilane being used as an internal standard.

λ_{max}^{EtOH} 238 mμ (ε 31000), ν_{max}^{KBr} 1705 cm^{-1} (20-ketone), 1680 and 1620 cm^{-1} (Δ^4-3-ketone), 1072 cm^{-1} (ether), was obtained. We shall report elsewhere the biological activities of the new progesterone analogue.



The great interest of hormone analogues of the progesterone-corticoid group with a 17α-hydroxymethyl substituent, led us to investigate pathways to such compounds. A theoretically simple approach would consist in the opening of the ether linkage of compounds of type II or III, but in spite of numerous experiments using a variety of methods and conditions, all attempts in this direction failed. Neither could we transform

such an ether to the corresponding hemiacetal and thence to a lactone (compare V) but we succeeded in synthesizing the desired products by photolysis of a nitrite of a 12α-hydroxy-17α-methyl steroid and the subsequent conversion of the reaction product to a 20⟶12 lactone.

We transformed in high yield in a model experiment, methyl 3-ethylenedioxy-12α-hydroxy-17α-methyl-5β-etianate (Ia) with nitrosyl chloride in pyridine (21) into the corresponding unstable nitrite Ib which could not be purified by crystallisation since during the process hydrolysis to the alcohol IIa occured. Irradiation with ultraviolet light in a pyrex vessel (21)[2] lead to a mixture of products, the ultraviolet spectrum of which is consistent with that of the nitrosodimer of an oxime (compare IV) (λ_{max}^{EtOH} 293 mμ). Since this mixture was not conveniently separated, it was hydrolized with methanolic hydrochloric acid, but again it proved impossible to isolate the aldehyde IVa or a derivative thereof. Oxidation with Jones' reagent gave a product from which the crystalline lactone V (m.p. 233-234°, $[\alpha]_D^{20}$ +24.5°) was readily separated in the pure state and characterized by its spectra [ν_{max}^{KBr} 1790 cm^{-1} (lactone), 1720 cm^{-1} (ester and lactone); δ 3.77 (s) (ester), 4.63 (t) (2 cps) (12β-H)], and by its elemental analysis. Hence the intermediate aldehyde IVa must have been present in the hemiacetal form IVA. The lactone V was converted with ethylene glycol and p-toluenesulfonic acid to its 3-ketal Va, m.p. 195-196.5°, which upon reduction with lithium aluminum hydride in tetrahydrofuran and subsequent acid hydrolysis in position 3, gave in good yield 17-bis-hydroxymethyl-5β-androstan-12α-ol-3-one (VI), m.p. 213°, $[\alpha]_D^{22}$ +33.0° [c = 1.04 dioxane], ν_{max}^{KBr} 3350, 3220cm^{-1} (broad hydroxy bands), 1720 cm^{-1} (3-ketone).

The application of this procedure to the synthesis of 17α-hydroxymethyl analogues of hormones of the progesterone-corticoid group will be reported at a later date.

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