1. Chemistry

1A. Synthesis of steroid derivatives

1. Fluorinated pregnenolone derivatives

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Treatment of the acetate of the unstable 20,20-dimethoxypregn-5-en-3β-ol with refluxing acetic anhydride gave a mixture of the acetates of 20-methoxypregna-5,17(20)-dien-3β-ol and 20-methoxypregna-5,20-dien-3β-ol. Fluorination of this mixture with perchloryl fluoride in pyridine afforded after fractionated crystallization 17α-fluoro-20-methoxypregna-5,20-dien-3β-ol acetate. Acid hydrolysis of the reaction mixture led, after chromatographic separation on Florisil, to 17α-fluoropregn-5-en-3β-ol-20-one acetate and 21-fluoropregn-5-en-3β-ol-20-one acetate. The 17α-fluoro-20-methoxypregna-5,20-dien-3β-ol acetate did not react further with perchloryl fluoride even under forcing conditions. Fluorination of 20-(ethyl-benzylamino)-pregna-5,17(20)-dien-3β-ol gave 17α,21-difluoropregn-5-en-3β-ol-20-one, exclusively.

2. Photochemical addition of primary amines to 16-dehydro-20-ketopregnanes: synthesis of androsteno (17α,16α-c)-2′-methyl-1′-pyrrolines and related compounds

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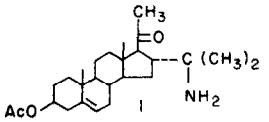
Brief irradiation of 16-dehydropregnenolone acetate in neat isopropylamine in a quartz vessel resulted in the formation of the photoadduct 1 and the photoreduction product, pregnenolone acetate. When the reaction was carried out in the dark for longer periods, only the normal Michael-adduct, 16α-isopropylaminopregnenolone acetate was formed. For preparative value to establish a carbon-carbon bond between 6-16 and the carbon bearing the nitrogen, the amine component has to be primary, attached to a secondary carbon. Under similar conditions 16-dehydroprogesterone gave the Δ^4-3-keto analog of 1. Treatment of 1 with piperidine and acetic acid in refluxing dioxane gave the [17α,16α-c]-1′-pyrroline 2 in good yield. Various reactions of this novel heterocyclic system will be described.



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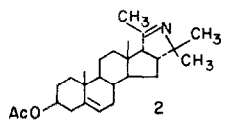

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3. Intramolecular catalysis in the hydroxylation of 7α-hydroxy steroids. A new method utilizing n.m.r.

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In order to study intramolecular catalysis, derivatives of methyl 7α-hydroxycholanate were synthesized and acetylation rates were determined by an n.m.r. method developed for the purpose. Substituents at C-3 include α-acetoxy, α-tosyloxy, α-mesyloxy, α-succinoyloxy, α-p-nitrobenzoyloxy, α-dimethylamino, β-chloro, oxo, ethylenedioxy, and ethylenedithia. Substituents at C-12 include α-hydroxy, α-methoxy, and oxo. The 3-esters were prepared by selective esterifications, the 3α-dimethylamino derivative by the Leuckart reaction on the corresponding 3-oxo compound, and the 12α-methoxy derivative by the action of methyl fluorosulfonate on methyl cholate 3,7-diacetate. Acetylations were carried out in n.m.r. tubes and rates were determined by measuring the relative intensities of angular methyl peaks, which shifted slightly on acetylation of the particular steroid. Most of the groups at C-3 afforded slight catalysis of 7α-hydroxyl acetylation. The 12α-hydroxyl group was most effective, and the absence of catalysis by a 12α-methoxyl group points toward protonation in the rate determining step. These results support a mechanism employing (where appropriate) bifunctional general acid-general base intramolecular catalysis.

4. Auto-oxidation of 3α,5-cyclo-5α-cholestan-6-one, 3α,5-cyclo-5α-cholestan-7-one and related compounds

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Auto-oxidation of 3α,5-cyclo-5α-cholestan-6-one in tert-butyl-alcohol in the presence of potassium tert-butoxide gave, after conversion of the acidic components into methyl esters and after chromatography, 7-hydroxy-3α,5-cyclo-5α-cholest-7-en-6-one (I), 3α,5-cyclo-6,7-seco-5α-cholestan-6,7-dioic acid dimethyl ester (II) as main products and 8-oxo-3α, 5-cyclo-B-nor-6, 8-seco-5a, 14β-cholestan-6-oic acid methyl ester (III), 7β-hydroxy-3α,5-cyclo-B-nor-5α-cholestan-7α-carboxylic acid methyl ester (IV) and 9α,14α-epoxy-8-oxo-3α,5-cyclo-B-nor-6,8-seco-5α-cholestan-6-oic acid methyl ester (V). The compounds II (main product), IV and V were also obtained by auto-oxidation of 3α,5-cyclo-5α-cholestan-7-one. Reactions of some androstane analogues will be described.

5. Steroid derived enantiomeric prostaglandin analogues Part 1: 5,13-Cyclo-4,8α-dimethyl-4,15-methano-12βH-prostaglandins

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Androstane derivatives have been transformed into ring A-seco steroid acids which are structurally identical with enantiomeric substituted prostaglandins bearing bridges between their side chains. As a consequence the C-(12–13) rotation of the prostaglandin analogues is fixed in the s-trans conformation. Stereochemistry will be discussed. The synthetic pathways will be described.