A New Method for Replacement of Hydroxyl by Chlorine or Bromine: Preparation of 11β-Halogeno-steroids

By (MISS) E. J. BAILEY, H. FAZAKERLEY, (MISS) M. E. HILL, C. E. NEWALL, G. H. PHILLIPPS,* L. STEPHENSON, and A. TULLEY

(*Glaxo Research Ltd., Greenford, Middlesex*)

Summary 11α-Hydroxy-19-nor-steroids react with *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine to give the 11β-fluoro-derivatives or, in presence of lithium chloride or lithium bromide, the 11β-chloro- and 11β-bromo-derivatives, respectively.

REACTION of *N*-(2-chloro-1,1,2-trifluoroethyl)diethylamine (1) with steroidal alcohols can give, among other things, the fluoro-steroid (normally with inversion) or a steroid olefin (with or without rearrangement).[1] 11α-Hydroxypregn-4-ene-3,20-dione has been reported to yield pregna-4,9 (11)-diene-3,20-dione, with only traces of 11β-fluoropregn-4-ene-3,20-dione,[2] but in contrast we have found that 11α-hydroxy-19-nor-steroids give good yields of 11β-fluoro-19-nor-steroids. Thus, treatment of the 11α-hydroxy-19-nor-steroids (3; R^1R^2 = O) and (3; R^1 = COMe, R^2 = OH) with the fluorinating reagent (1) in tetrahydrofuran gave the corresponding 11β-fluoro-compounds (4; R^1R^2 = O, X = F) and (4; R^1 = COMe, R^2 = OH, X = F) in up to 45% yield. The 11β-configuration was assigned to the fluoro-substituents on the basis of ^{1}H n.m.r. spectra (for solutions in deuteriochloroform, using a Varian A60 spectrometer); for example, that of the 17-ketone (4; R^1R^2 = O, X = F) showed signals at τ 4·95 (d, $J_{H\text{-}F}$ 48 Hz) for the equatorial 11-proton and at τ 8·93 (d, $J_{H\text{-}F}$ 2 Hz) for the C-18 protons, which undergo long-range splitting with the axial 11β-fluorine.[2,3]

There have been no previous reports of 9-unsubstituted 11β-halogeno-19-nor-steroids and, since we found that 11β-fluoro-compounds possessed hormonal activity (see below), we were interested to prepare analogous compounds with other halogens. Conversion of alcohols (ROH) into fluorides (RF) by reagent (1) is considered to involve attack on the reactive intermediate (2) by the fluoride ion eliminated during the conversion of (1) into (2). There is evidence[1] that methyl cyanide, used as solvent, can compete with fluoride ion for intermediate (2) and it seemed possible, therefore, that the more nucleophilic chloride or bromide

ions might also compete in this way. Indeed, reaction of (3; R^1R^2 = O) with (1) and an excess of lithium chloride in tetrahydrofuran at 0° gave the 11β-chloro-compound (4; R^1R^2 = O, X = Cl) in 85% yield: the corresponding 11β-bromo-compound (4; R^1R^2 = O, X = Br) was formed in 57% yield by use of lithium bromide in methylene chloride. The halogeno-compounds (4; R^1 = COMe, R^2 = OH, X = Cl or Br) in the 17α-hydroxy-19-norpregnane series were prepared similarly, the tertiary 17α-hydroxy-group being unaffected.

The 11β-halogeno-substituents were stable during a variety of reactions elsewhere in the molecule. For example, the 17-ketones (4; R^1R^2 = O, X = F, Cl, or Br) were converted *via* their enol ethers (5; R^1R^2 = O, R^3 = Et) into the ethynyl carbinols (5; R^1 = OH, R^2 = C:CH, R^3 = Et) and thence into the 11β-halogeno-derivatives (4; R^1 = OH, R^2 = C:CH, X = F, Cl, or Br) of the orally active progestagen, norethisterone. Again, the 17α-hydroxy-19-norpregnan-20-ones (4; R^1 = COMe, R^2 = OH, X = F, Cl, or Br) were converted into the enol diacetates (5; R^1 = COMe, R^2 = R^3 = OAc), which were selectively hydrolysed to the 11β-halogeno-derivatives (4; R^1 = COMe, R^2 = OAc, X = F, Cl, or Br) of 17α-acetoxy-19-norprogesterone. Further, the enol diacetate (5; R^1 = COMe, R^2 = R^3 = OAc, X = Cl) was chlorinated to give a mixture of 6-chloro-Δ^4-3-ketones (6), the enol ethyl ether (7) from which was dehydrogenated by manganese dioxide[4] to the 6-chloro-$\Delta^{4,6}$-3-ketone (8), the 11β-chloro-19-nor-analogue of the very active progestagen, 17α-acetoxy-6-chloropregna-4,6-diene-3,20-dione ('Chlormadinone acetate').

These compounds showed oral progestational activity in rabbits by the McPhail test. The 11β-chloro-compounds were usually more active than their 11β-fluoro- or 11β-bromo-analogues and considerably more active than the corresponding 11-unsubstituted compounds. In particular, the 19-norpregnanes (4; R^1 = COMe, R^2 = OAc, X = Cl) and (8) rank with the most active progestational compounds so far reported.

Although, as mentioned at the outset, treatment of 11α-hydroxy-10-methyl-steroids with the fluorinating reagent (1) results almost entirely in elimination, our experiments in the 19-nor-series encouraged us to hope that substitution by chlorine might compete more successfully with elimination. In fact, a number of 11α-hydroxy-10-methyl-steroids react with reagent (1) and lithium chloride to give the 11β-chloro-analogues in 4—40% yield, the Δ^9-olefins usually being the major product.

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