Enolates of 17,20:20,21-Bismethylenedioxyprednisone[1]

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Summary The factors governing enol anion formation from 17,20:20,21-bismethylenedioxyprednisone (prednisone BMD) at C-6 and C-9 have been investigated by quenching with benzoic anhydride; kinetically controlled enolisation occurs at C-6 followed by rearrangement, catalysed by unenolised ketone, to the C-9 anion.

THE smooth fluorination of vinyl esters with CF_3OF, which we have recently reported,[2] suggested that application of this reaction to 9(11)-vinyl esters, such as (Ia), would provide an easy entry to the medicinally important 9α-fluoro-corticosteroids.[3] Treatment of prednisone-BMD (II) with either triphenylmethyl- or ethynyl-sodium, followed by reaction with benzoic anhydride, gave a mixture of (II) and variable amounts of both the 1,3,5-trienol-benzoate (IIIa), m.p. 226–228°, $[\alpha]_D$ ($CHCl_3$) −182°, and the hitherto unknown 9(11)-enol-benzoate (Ia), m.p. 290—293°, $[\alpha]_D$ +33·4°. Each enol ester reverted to (II) on treatment with mild alkali). Although the feasibility of our route was confirmed by fluorination studies, poor yields and variable proportions of the isomeric esters (Ia) and (IIIa) demanded a study of the relationship of (II), a suitable base, and the enolates (Ib) and (IIIb) expressed by capture to afford (Ia) and (IIIa). We were at this point informed by Dr. M. Tanabe of his work[4] along similar lines using sodium bistrimethylsilylamide (IVa).[5] The advantageous properties of (IVa)[4] and the availability of lithium bismethylsilylamide[5] (IVb), which differs from (IVa) only by virtue of the associated cation, rendered these bases particularly suitable for the present studies.

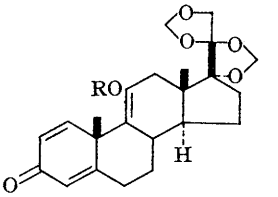
A priori one may envision three possible relationships among (II), (III), and (I): direct and independent bimolecular enolization (eq. 1),

(1) (II) + (IV) → (Ib) —//→ (IIIb)
(II) + (IV) → (IIIb) —//→ (Ib)

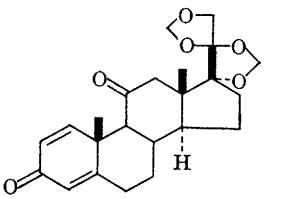
or the enolization and rearrangement in the sense of either eq.[5] 2 or 3

(2) (II) + (IV) → (Ib) → (IIIb)
(3) (II) + (IV) → (IIIb) → (Ib)

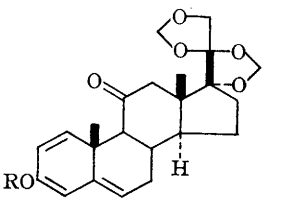
In addition one might consider, in the case of eq. 3, unimolecular isomerization (transfer of hydrogen from 9α to 6α) as well as reaction of enolate (IIIb) with (II) to afford the isomeric enolate (Ib) and regenerated (II).[6]



(I) a; R=Bz, b; R=Na



(II)



$(Me_3Si)_2NX$

(IV) a; X=Na, b; X=Li

(III) a; R=Bz, b; R=Na, c; R=Li

While treatment of (II) with a modest excess of the sodium base (IVa) followed by quenching with Bz_2O afforded largely the 9(11)-enol benzoate (Ia) ratio (Ia) : (IIIa) = 2 : 1 a similar sequence involving the lithium base afforded

only the 3-enol-benzoate (IIIa). Use of an insufficient quantity of (IVb) gave a mixture of (IIIa) and (II). No (Ia) was evident. This observation, taken with the known reluctance (relative to sodium enolates) of lithium enolates to isomerize,[6] pointed to the mechanism expressed in eq. 3. Confirmation was provided by the following experiments. The reaction of (II) and a modest excess of (IVa) at room temperature when quickly (< 2 min., before complete anion formation) quenched with Bz_2O gave lower ratios of (Ia) : (IIIa) (R = 0·4 : 1) than if quenching were postponed (>5 min.), giving time for anion transfer. The enolization and isomerization reactions could be cleanly separated at *ca.* — 78°. The reaction of (II) and (IVa) followed by quenching with Bz_2O at that temperature afforded only (IIIa). Incubation at room temperature of a solution of the 3-sodium-enolate (IIIb) [formed by the reaction of (II) and (IVa) at —78°] followed by quenching with Bz_2O, also afforded only (IIIa), demonstrating that the changed course of the reaction was not a reflection of a temperature dependence of the equilibrium (IIIb) ⇌ (Ib) and that the 3-sodium-enolate (IIIb) *was stable in the absence of un-ionised dione* (II).

Finally, it was observed that addition of a catalytic quantity (25%) of (II) to a solution of (IIIb) maintained at room temperature catalysed the conversion of (IIIb) into (Ib) as evidenced by the isolation of both (IIIa) and (Ia) (R = 1 : 1). This establishes the bimolecular nature of the isomerisation. It is thus apparent that the enolization proceeds with transfer of a proton from C-6 of the steroid (II) to the base (IV) yielding initially a 3-enolate (IIIb or c). The 3-lithium-enolate (IIIc) is stable, but the corresponding 3-sodium-enolate (IIIb), in the presence of (II) may rearrange to the 11-sodium-enolate (Ib). The equilibrium for this reaction lies far to the right. Recognition of these events leads to a synthetic mastery of the reaction: slow addition of (II) to a solution containing slightly more than an equivalent of (IVa) gives mainly the 3-enolate (IIIb) [isolated as (IIIa)] (>80%) while slow addition of slightly less than 1 equiv. of (IVa) to a solution of (II) gives the 11-enolate (Ib) [isolated as the much desired (Ia), 80%]. The rational preparation of specific enolates from steroidal 1,4-diene-3,11-diones is of synthetic value. Fluorination with CF_3OF of (IIIa) and of (Ia) affords 6-fluoro- and 9-fluoro-steroids respectively.

All new compounds afforded appropriate micro-analytical values and exhibited i.r. and n.m.r. spectra which were unexceptional and consistent with the assigned structures.

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[1] For previous paper in this series, see D. H. R. Barton, N. J. A. Gutteridge, R. H. Hesse, and M. M. Pechet, *J. Org. Chem.*, 1969, **34**, 1473.
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