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A SYNTHESIS OF 11β-HYDROXY-STEROIDS(1)

D.H.R. Barton and N.K. Basu

Research Institute for Medicine and Chemistry, Cambridge, Mass.

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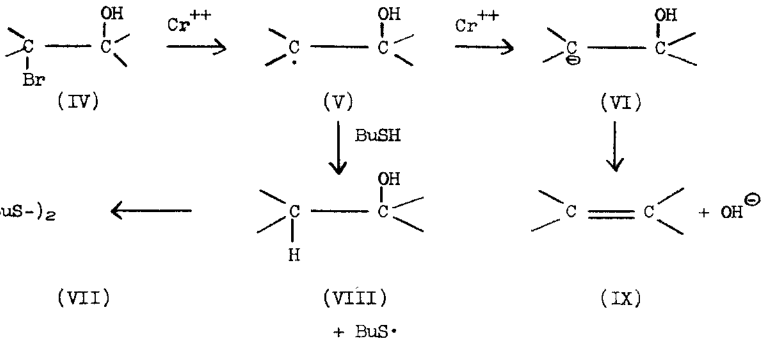
We wish to report a new method for the conversion of the readily available 9α-bromo-11β-hydroxy-steroids into the medicinally important 11β-hydroxy-steroids in good yield. In essence, the method consists of reducing 9α-bromo-11β-hydroxy steroids with chromous salts in the presence of a transfer donor of radical hydrogen, suitably a thiol. Previous attempts(2) to affect this reduction gave unsatisfactory results.

Treatment of 9α-bromo-11β-hydroxyprogesterone(2) Ia, with chromous acetate (5 equivs.) in dimethylsulphoxide containing butane-1-thiol (7.5 equivs.) under carbon dioxide at room temperature for 6 - 13 hr., gave 11β-hydroxyprogesterone(4) Ib in 80% yield. No 9(11)-dehydroprogesterone Ic, the normal product(2) of reduction, was isolable from this reaction. Similarly, 9α-bromocortisol 21-acetate(3), 9α-bromoprednisolone 21-acetate(5) and 17,20:20,21-bismethylenedioxy-9α-bromocortisol(6) afforded cortisol 21-acetate (78%), prednisolone 21-acetate (74%) and 17,20:20,21-bismethylenedioxycortisol (80%) respectively.

In the absence of butane-1-thiol the reduction proceeded in a different manner. The bromohydrin Ia gave 5,9-cyclo-11β-hydroxypregnan-3,20-dione II, m.p. 138-143°, $[\alpha]_D$ -44° (58%) and the 9(11)-olefin Ic (5%). The constitution of II was based on its spectral properties, on analogy(7) and on its conversion by oxidation with chromium trioxide in pyridine to 11-ketoprogresterone, no doubt formed by isomerisation of III (see arrows).

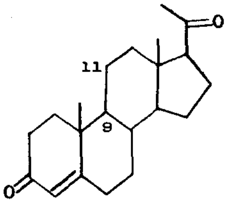
Similar results were obtained in dimethylformamide as solvent. In tetrahydrofuran and **N**-methylpyrrolidone the cyclopropane II was accompanied by the 9(11)-olefin Ic and some 11β-hydroxyprogesterone Ib.

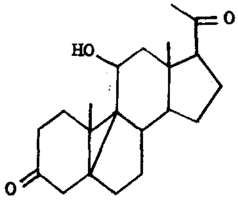
The success of this work, initiated in 1962, was the premise(8) that chromous ion reduction of a bromohydrin (IV) would proceed in two stages as follows:

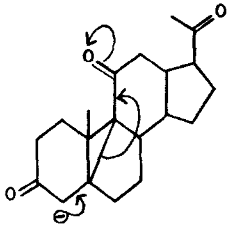


Thus a radical intermediate (V) would be the first product of reduction. Further reduction of this radical would furnish the anion (VI), which by elimination would give the normal product (IX) of bromohydrin reduction(2). The step (VI) ⟶ (IX) might well be acid catalysed and this we have also demonstrated. The radical (V) could, in principle, be captured by a ready transfer donor of radical hydrogen such as thiol. In the particular case of butylthiol the BuS· radical would be the other product, which should then dimerise to $(BuS)_2$ (VII). In a large scale reduction we showed 100% formation of $(BuS-)_2$. A blank experiment(9) under the same conditions in dimethylsulphoxide gave rise to only a minor amount of $(BuS-)_2$. Other sources of radical transfer such as MeSH, EtSH, PhSH, 1,4-cyclohexadiene, 1-benzyl-1,4-dihydronicotinamide, and H_3PO_2 also served to capture radical (V) with formation of (VIII). All experiments were carried out on the 9α-bromo-11β-hydroxy-compound Ia.

Further work on the scope of the reaction is in progress(10,11).







Ia, 9α-bromo-11β-hydroxy- II III

Ib, 11β-hydroxy-

Ic, 9(11)-dehydro-

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10 All new compounds had ultraviolet, infrared and nuclear magnetic resonance spectra in accord with the structures assigned and gave satisfactory analytical results.

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