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INSERTION OF OXYGEN ATOM IN STEROID FRAMEWORKS —— A NEW METHOD OF TRANSFORMATION OF HYDROXYSTEROID INTO OXASTEROID[1)]

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A two-step transformation of saturated hydroxysteroids into oxasteroids is described; the reaction involves photo-reaction of the hypoiodites of the hydroxysteroids generated with mercury(II) oxide and iodine to give isomeric formyl esters [e.g., 2 and 3], which are cyclized to oxasteroids [e.g., 4 and 5] with sodium borohydride.

We have recently reported unusual photoinduced radical rearrangement of cholesteryl hypoiodite in the presence of an excess of iodine oxide which led to form 2-iodo-A-nor-2,3-secocholest-5-en-3-yl formate in a substantial yield.[2)] This formate was then readily transformed into 3-oxacholest-5-ene by the treatment with sodium borohydride.[2)]

We now wish to report that this new reaction can be applied to a two-step transformation of a saturated hydroxysteroid into rather inaccessible oxasteroids having the size of the oxygen ring same as that of the starting ring carrying hydroxy group.

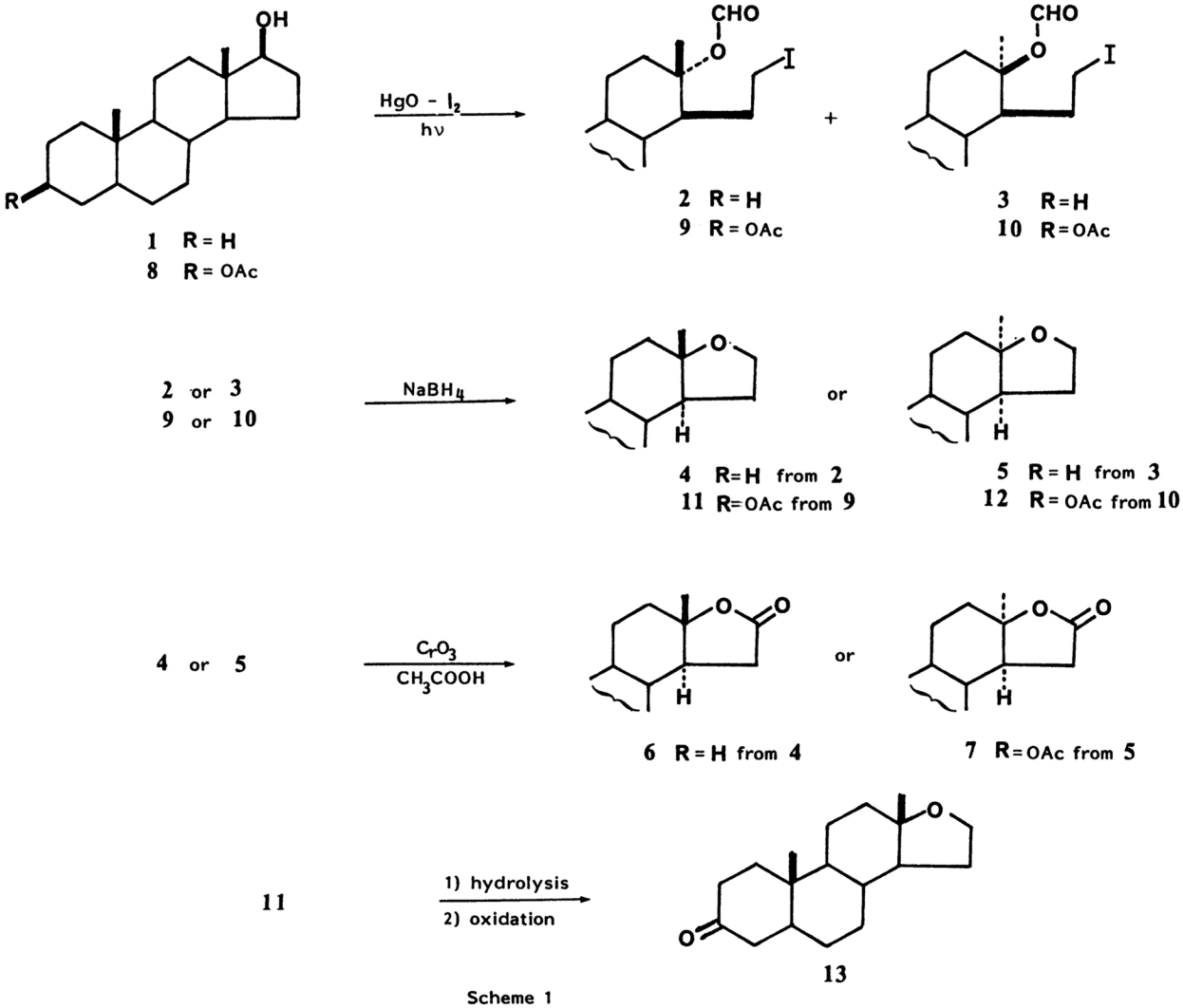
Thus, 5α-androstan-17β-ol(1) (600 mg) in benzene (108 ml) containing mercury (II) oxide (1.1415 g) and iodine (1.656 g) in a Pyrex vessel was irradiated with a 100-W high pressure mercury arc for 2 h under a nitrogen atmosphere to give a mixture of 16-iodo-D-nor-16,17-seco-5α-androstan-13β-yl formate (2) and its 13β-isomer (3). The yield of 3 (preparative TLC) was 44% (Scheme 1).
The mixture in THF containing sodium borohydride was heated under reflux for 3.5 h to give 17-oxa-5α-androstane(4) (72%), mp 90.5-91.5 °C, (acetone-methanol) [MS (70 eV) m/z, (rel intensity) 262 (M^+, 1.5%), 247 (M^+-CH_3, 100%); IR (Nujol) 1167, 1027, and 998 cm^{-1}; ^1H NMR (90 MHz $CDCl_3$), δ = 0.80 (3H, s, 19-H), 0.97 (3H, s, 18-H), 3.86 (t, J = 4 Hz) and 3.96 (t, J = 4 Hz) (2H, 16-H)] and amorphous 17-oxa-5α,13α-

androstane(5), (9%) [Found: m/z, 262.2284. Calcd for $C_{18}H_{30}O$: M, 262.2294. MS (70 eV) m/z, (rel intensity) 262 (M^+, 2.4%), 247 (M^+-CH_3, 100%); IR (neat) 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.71 (3H, s, 19-H), 1.08 (3H, s, 18-H), and two doublets centred at 3.87 and 3.97 (each 1H, d, J = 6 and 10 Hz, 16-H)]. Oxidation of 4 (60 mg) in acetic acid (10 ml) and water (1.5 ml) with chromium trioxide (230 mg) at 50-70 °C gave 17-oxa-5α-androstan-16-one(6), (92%), which was identical with a specimen prepared by Baeyer-Villiger oxidation of D-nor-5α-androstan-16-one,[3] thus confirming the stereochemistry of 13-methyl group of 4 as β. Similar oxidation of cyclic ether 5 gave 17-oxa-5α,13α-androstan-16-one (7), mp 94-96 °C, [Found: m/z, 276.2077. Calcd for $C_{18}H_{28}O_2$: M, 276.2087. MS (70 eV) m/z, (rel intensity) 276 (M^+, 5.3%), and 261 (M^+, 5.3%) and 261 (M^+-CH_3, 100%); IR (neat), 1770 (five-membered lactone), 1155, 1060, and 928 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 0.68 (3H, s, 19-H), and 1.27 (3H, s, 18-H)] (Scheme 1).

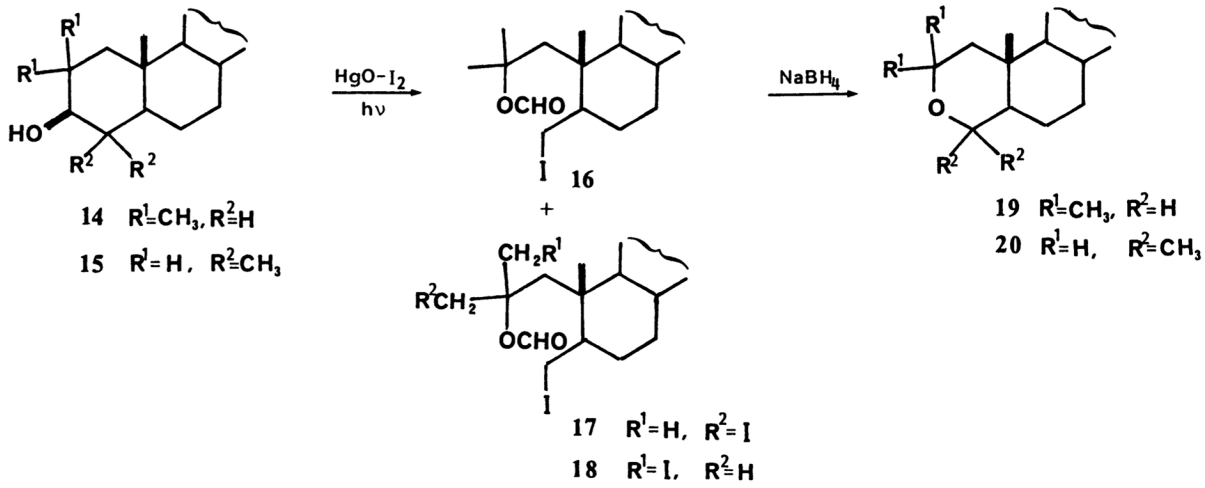
17-oxa-5α-androstan-3-one(13),[4] which is an almost only five-membered D-ring oxasteroid ever described and has been prepared from 5α-androstan-3-one via 8 steps could be obtained in a parallel manner via 4 steps from 5α-androstan-3α,17β-diol-3-acetate(8). Thus, the reaction of 8 under the conditions described above gave a mixture of isomeric formates 9 and 10 (60% yield). This mixture was transformed into a 9 : 1 mixture of isomeric oxasteroids 11 and 12 (37% yield). Separation of the mixture into its components by means of preparative TLC and hydrolysis of 11 with methanolic potassium hydroxide gave 17-oxa-5α-androstan-3β-ol, double mp 112-114 °C and 135-139 °C. Its oxidation with chromium trioxide-pyridine gave 13, mp 108-110 °C (Lit.[4] mp 109-110 °C).

Six-membered oxasteroids can be similarly prepared by this method. Irradiation of 2,2-dimethyl-5α-cholestan-3β-ol(14), mp 143.5-145.0 °C, prepared via two steps from 2,2-dimethylcholest-4-en-3-one,[5] in benzene containing mercury(II) oxide and iodine gave 2,2-dimethyl-2-formyloxy-3-iodo-5α-cholestane(16) (51% yield), mp 110-111.5 °C, [Found: m/z, 559.2979. Calcd for $C_{29}H_{52}O_2I$: M, 559.3010. MS (70 eV) m/z, (rel intensity) 559 (M^+, 58.6%), and 513 (M^+-OCH_2O, 100%); IR 1732 (OCHO), 1173, and 1150 cm^{-1} (formate C-O); ^1H NMR ($CDCl_3$) δ = 0.67 (3H, s, 18-H), 0.74 (3H, s, 19-H), 1.62 and 0.71 (each 3H, s, 2,2-dimethyl), 3.82 (1H, d, J = 9 Hz, 3-H), 2.89 (1H, dd, J = 9 and 10 Hz, 3-H) and 8.24 (1H, d, OCHO)], together with a mixture of two diiodides 17 and 18 (13% yield in total) as the minor products.

The formate 16 was again smoothly transformed into 2,2-dimethyl-3-oxa-5α-



Scheme 1



Scheme 2

cholestane(19), mp 110-110.5 °C, [Found: m/z, 402.3897. Calcd for $C_{28}H_{50}O$: M, 402.3862. MS (70 eV) m/z, (rel intensity) 402 (M^+, 0.2%), and 387 (M^+-CH_3, 100%); IR 1073 cm^{-1} (C-O-C), ^1H NMR ($CDCl_3$) δ = 0.64 (3H, s, 18-H), 0.98 (3H, s, 19-H), 1.19 and 1.26 (each 3H, s, 2-dimethyl), and 3.24-3.66 (2H, m, 4-methylene)] in 64% yield by heating under reflux in THF containing sodium borohydride.

4,4-Dimethyl-3-oxa-5α-cholestane(20), mp 98-100 °C, can analogously be prepared via two steps from 4,4-dimethyl-5α-cholestan-3 -ol(15)[6] in a 22% yield.

A survey of the literature reveals that only a limited number of oxasteroids have been known while numerous azasteroids have been synthesized.[7] The present method thus should find application in a facile transformation of hydroxysteroids into oxasteroids under virtually neutral conditions. A further scope and the limitation of this method are under investigation and will be reported at a later date.

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