6α-Fluoromethyl Steroids

A. L. NUSSBAUM, M. KIRTLEY, A. V. MARESCO, AND E. P. OLIVETO

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The accessibility of certain novel hydroxymethyl derivatives of steroids by means of the hydroformylation reaction,[1,2] coupled with the current interest in fluorinated steroid hormonal analogs led us to apply the general method of Tannhauser, Pratt, and Jensen[3] to the synthesis of 6α-fluoromethylpregnane derivatives.

Conversion of 6α-hydroxymethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (I) to the tosylate (IIa) has already been reported.[1] Attempts to improve the yield by raising the reaction temperature led instead to the corresponding chloride (IIb). Treatment of the tosylate with sodium iodide, or direct conversion of the alcohol (I) by the method of Landauer and Rydon,[4] gave 6α-iodomethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (IIc). The material could be used in crude form in the next step, conversion to the fluoride (IId) by means of silver fluoride in aqueous acetonitrile.[3,5] This conversion required more drastic conditions than the corresponding reaction at C-21 of iodides activated by the neighboring keto group at C-20. It was found that the best results were obtained when the silver fluoride reagent was freshly prepared[6] *in situ*, but even then the yields were considerably lower than in the side chain examples.

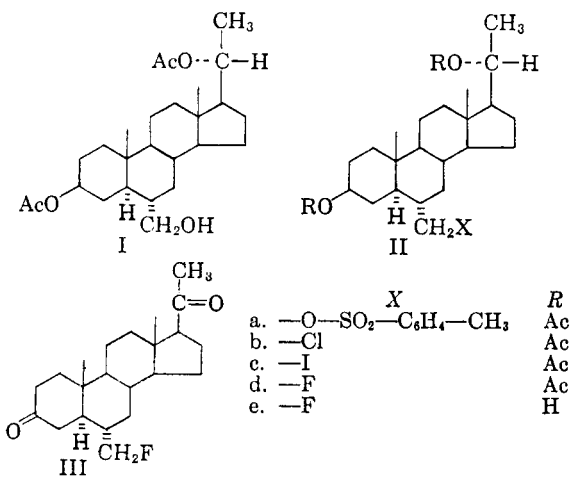

CHART I

For further characterization, diacetate IId was saponified to the diol (IIe) and the latter oxidized to the dione (III).

EXPERIMENTAL[7]

6α-Iodomethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (IIc). *A. From 6α-hydroxymethyl 5α-pregnane-3β,20β-diol 3,20-diacetate* (I). Triphenyl phosphite methiodide was prepared after the manner of Landauer and Rydon[4] by allowing 25.1 ml. of triphenyl phosphite and 7.7 ml. of methyl iodide to interact for 36 hr. at reflux temperature. The resulting solid was covered with 600 ml. of anhydrous ether, and 9.9 g. of 6α-hydroxymethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (I) was added. The resulting solution was refluxed for 90 min. and then allowed to stir overnight at room temperature. The decanted solution was extracted with 5% aqueous sodium hydroxide solution and washed with water, dried over sodium sulfate and concentrated to a red oil. Chromatography on 400 g. of Florisil gave 5.7 g. of solid material from the benzene eluates. This crude 6α-iodomethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (IIa) could be used directly in the next step.

For characterization, a small amount was recrystallized from acetone-hexane to analytical purity, m.p. 152–154°. Beilstein positive.

Anal. Calcd. for $C_{26}H_{41}O_4I$: I, 23.31. Found: 22.98.

B. From 6α-tosyloxy-5α-pregnane-3β,20β-diol 3,20-diacetate (IIa). Tosylate IIa (100 mg.) was dissolved in 20 ml. of acetone and 250 mg. of sodium iodide was added. The mixture was refluxed for 3 hr., concentrated *in vacuo* to a small volume and diluted with water. The resulting oil was extracted with methylene chloride, the extract washed with water and dried over sodium sulfate, concentrated and crystallized from hexane to give 67 mg. of the iodo derivative IIc, identical in infrared spectrum with the material described above.

6α-Fluoro-5α-pregnane-3β,20-diol 3,20-diacetate (IId). Silver nitrate (115 g.) was dissolved in a minimum of water and added to a solution of 28 g. of sodium hydroxide in 600 ml. of water. The resulting silver oxide was filtered, dried well, and added to 28.3 ml. of 48% aqueous hydrofluoric acid and 29 ml. of water in polyethylene beaker. The resulting suspension was stirred for 0.5 hr. and then filtered into a reaction vessel wrapped in aluminum foil and containing 900 ml. of acetonitrile and 106 ml. of water. To the white suspension, a solution of 4.0 g. of iodo steroid IIc in 60 ml. of acetonitrile was added. The immediate formation of a brown precipitate was observed. The suspension was refluxed for 1.5 hr. and then allowed to stand overnight. Filtration through Supercel and simultaneous charcoal treatment were followed by concentration *in vacuo* to a small volume and extraction with methylene chloride. The resulting organic extract was washed with aqueous ammonium hydroxide, sodium thiosulfate, and water, dried, and concentrated. The residual oil was chromatographed on 60 g. of Florisil. The benzene eluates gave 1.25 g. of crude 6α-fluoromethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (IId). Crystallization from hexane gave 787 mg., m.p. 172–175°. An analytical sample was prepared by repeated recrystallization from isopropyl ether. It had m.p. 175–177°.

Anal. Calcd. for $C_{26}H_{41}O_4F$: C, 71.52; H, 9.48; F, 4.35. Found: C, 71.47; H, 9.48; F, 4.2.

(1) A. L. Nussbaum, T. L. Popper, E. P. Oliveto, S. Friedman, and I. Wender, *J. Am. Chem. Soc.*, **81**, 1228 (1959).

(2) P. F. Beal, M. A. Rebenstorf, and J. E. Pike, *J. Am. Chem. Soc.*, **81**, 1231 (1959).

(3) P. Tannhauser, R. J. Pratt, and E. V. Jensen, *J. Am. Chem. Soc.*, **78**, 2658 (1956).

(4) H. N. Rydon and S. R. Landauer, *Chem. and Ind.*, 313 (1951); S. R. Landauer and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).

(5) An attempt to convert chloride IIb in this manner gave back the starting material.

(6) E. D. Bergmann and I. Shalak, *J. Chem. Soc.*, 1418 (1959).

(7) All melting points were taken on a Kofler microstage. Analyses and optical data were obtained by the Physical Chemistry Department of Schering Corporation, and some of the former by Schwarzkopf Microanalytical Laboratories

Further eluates with 10% ether-benzene gave 195 mg. of 6α-hydroxymethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (I), the starting material.

6α-Fluoromethyl-5α-pregnane-3β,20β-diol (IIc). The foregoing diacetate (IId, 250 mg.) was saponified by refluxing for 3 hr. in 45 ml. of 5% methanolic potassium hydroxide. The solution was neutralized with glacial acetic acid and concentrated to a small volume. Addition of water and filtration gave 193 mg. of the diol. Recrystallization from acetone-hexane gave an analytical sample, m.p. 199–201°.

Anal. Calcd. for $C_{22}H_{37}O_2F$: C, 75.00; H, 10.58. Found: C, 75.08; H, 10.20.

6α-Fluoromethyl-5α-pregnane-3,20-dione (III). The fluorodiol (IIc, 180 mg.) was dissolved in 40 ml. of distilled acetone and titrated to a permanent brown color with 8*N* Kiliani acid. Dilution with 200 ml. of ice water precipitated the steroidal dione (III). Filtration gave 145 mg. of crude product. Recrystallization from acetone-hexane gave an analytical sample, m.p. 136–137°.

Anal. Calcd. for $C_{22}H_{33}O_2F$: C, 75.85; H, 9.54. Found: C, 75.51; H, 9.30.

6α-Chloromethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (IIb). 6α-Hydroxymethyl-5α-pregnane-3β,20β-diol 3,20-diacetate (1.0 g.) was dissolved in 12 ml. of pyridine and treated with 2.1 g. of *p*-toluenesulfonyl chloride. The solution was refluxed for 3 hr., poured into excess ice water, and the resulting solid was filtered and washed with water until free of pyridine. After air-drying, the product had m.p. 180–185° (previous transition in the 170's), weight 383.3 mg. Recrystallization from methanol gave an analytical sample, m.p. 186–187.5°, $[\alpha]_D^{23}$ +45.0 (chloroform).

Anal. Calcd. for $C_{26}H_{41}O_4Cl$: C, 68.92; H, 9.12; Cl, 7.83. Found: C, 69.24; H, 9.00; Cl, 7.99.

NATURAL PRODUCTS RESEARCH DEPARTMENT
SCHERING CORP.
BLOOMFIELD, N. J.

The Epimeric 6-Hydroxyestrones[1]

R. Y. KIRDANI AND W. R. SLAUNWHITE, JR.

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There are several references in the biochemical literature to 6-hydroxyestrone,[2–4] but no chemical characterization has been reported. We have prepared one of the epimeric 6-hydroxyestrones to which we assign the *beta* configuration, and have demonstrated a practical route to the *alpha* epimer. Our assignment of configurations is based on those recently reported by Wintersteiner and Moore.[5] Tentatively these authors assigned the *alpha* configuration to the epimer prepared by sodium borohydride reduction of 6-ketoestradiol, and the *beta* configuration to the derivative obtained by catalytic hydrogenation of the 6-keto compound. Similarly, Marrian and Sneddon[6] assigned the *alpha* configuration to the epimer they prepared by sodium borohydride reduction of 6-ketoestriol.

6-β-Hydroxyestrone was obtained by catalytic hydrogenation of 6-ketoestrone, allowing only one mole equivalent of hydrogen to be consumed. The discrepancy between the quantity of hydrogen consumed and yield of 6-β-hydroxyestradiol reported by Wintersteiner and Moore[5] was also observed in the present instance. Analysis of a countercurrent distribution by ultraviolet and infrared spectroscopy and by weight measurements also gave evidence for the presence of 6-ketoestrone (starting material), estrone (hydrogenolysis product), and material that was transparent to ultraviolet light and was, therefore, probably an estrane.

In analogy to the preparation of 6-α-hydroxyestradiol by Wintersteiner and Moore,[5] an attempt to prepare 6-α-hydroxyestrone by sodium borohydride reduction was not successful since the 17-carbonyl function of 6-ketoestrone was reduced first. Although the 17-hydroxyl of 6-α-hydroxyestradiol is blocked from one side by the angular methyl group, it has not been possible to use this triol as starting compound for the preparation of the estrone derivative. In an effort to exploit any possible difference in reaction rates of the 6 and 17 hydroxyl functions, both estradiol-17β as model compound and 6-α-hydroxyestradiol were allowed to react with ethyl chlorocarbonate and with trimethylacetyl chloride. The bulkiness of these two entering groups should emphasize small differences in reactivity due to conformation or steric hindrance.

In practice no appreciable difference was observed. The 17-hydroxyl group of estradiol was completely esterified in eight hours at 37°. Obviously the reactivity of the 17-hydroxyl is so great that it precludes a selective esterification of the 6-hydroxyl.

A synthesis by which 6-α-hydroxyestrone can be obtained was devised by preparing 17-ethylenedioxy-6-β-hydroxyestrone, which by Oppenauer oxidation gave the 6-keto derivative. Although the preparation of 6-α-hydroxyestrone from the latter compound can be readily accomplished by sodium borohydride reduction and hydrolysis, it was not possible to obtain an analytically pure sample because 6-β-hydroxyestrone was available in only very limited quantities. Good evidence was, however, obtained by ultraviolet and infrared analysis that the reaction product was the desired compound. The absorption maxima in the ultraviolet were identical with those of the 6-β-hydroxyestrone, and the molecular extinction coefficients were nearly identical. There was also a very close resemblance of infrared spectra.

(1) From the thesis submitted by Rashad Y. Kirdani for the degree of doctor of philosophy from the Roswell Park Division of the University of Buffalo Graduate School of Arts and Sciences.

(2) G. C. Mueller and G. Rummey, *J. Am. Chem. Soc.*, **79**, 1004 (1957).

(3) H. Breuer, L. Nocke, and R. Knuppen, *Naturwissenschaften*, **45**, 397 (1958).

(4) H. Breuer, L. Nocke, and R. Knuppen, *Z. physiol. Chem.*, **315**, 72 (1959).

(5) O. Wintersteiner and M. Moore, *J. Am. Chem. Soc.*, **81**, 442 (1959).

(6) G. F. Marrian and A. Sneddon, *Biochem. J.*, **74**, 430 (1960).