A NEW SYNTHETIC ROUTE TO 2-HYDROXYL STEROIDAL ESTROGENS VIA ACETYLATION AND DAKIN OXIDATION

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ABSTRACT

This paper describes a new two-step synthetic route to 2-hydroxy estrogens from either estrone or estradiol, via 2-acetylation followed by Dakin oxidation. This approach is characterized by its simplicity and excellence of yield.

INTRODUCTION

A number of tests, both *in vivo* and *in vitro*, indicate that 2-hydroxy estrogenic compounds, especially 2-hydroxyestrone, are metabolic products of estrogenic steroids (1). Current investigations of the physiological properties, endocrinology and clinical application of compounds of this kind have been evoking widespread interest.

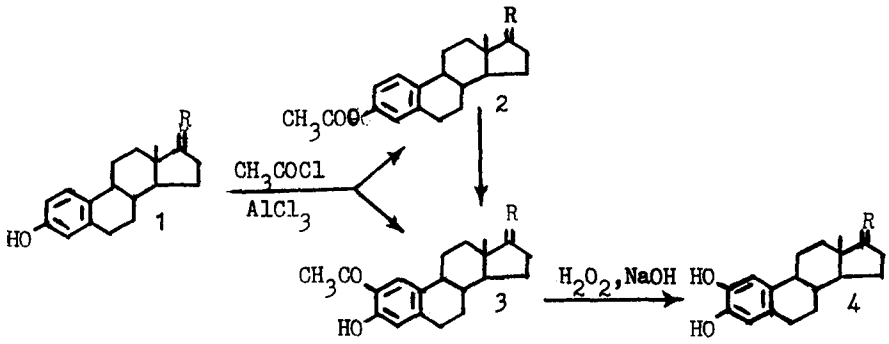
Although there are many synthetic routes to orthohydroxy estrogenic steroids, few if any can be considered entirely satisfactory(2-13). Available methods, of which the radical benzoyloxylation of Michiya *et al.* (8) and the inverse oxidation of aminophenol by Stubenrauch and Knuppen (12) are representive, suffer in common from numerous steps and low yields.

This communication describes a new two-step synthetic route to 2-hydroxyestrogens from either estrone or estradiol as the starting material, via 2-acetylation followed by Dakin oxidation. It seems to us that this route is superior to any thus far reported for the partial synthesis of this type of steroidal estrogens.

The literature includes several reports of acetylation on ring A of estrogenic steroids. Hoehn (14) and Crabbe *et al.*(15) effected direct acetylation by the action of acetyl chloride on estradiol in the presence of aluminum chloride, resulting in the formation of 2-acetyl estradiol 17-acetate. We have modified their procedure of experiment and reaction

conditions thus making the yield higher and steady at around 57%. On the other hand, Nambara et al. effected a Fries rearrangement of the 3-acetate of estrone (5). Nambara et al. and Hoehn obtained the 2-acetyl estrone by acetylation of the corresponding 3-methyl ether (5, 14). We find that direct acetylation of estrone generates 2-acetyl estrone in much higher yield than so far reported in the literature without having to prepare an ester or ether derivative beforehand. The main by-product of these reactions are the 3-acetates of estrone or estradiol, indicating that C-acetylation and O-acetylation are concurrent reactions. The O-acetylation product could be partially converted into the desired C-acetylation product at elevated temperature. These reactions are regioselective because of the C_6 steric interference.

The Dakin reaction has not been employed previously for the synthesis of estrogenic compounds. In the present investigation 2-acetyl estrogenic steroids were treated at room temperature with an alkaline solution of hydrogen peroxide in diglyme, resulting in the formation of 2-hydroxyl estrogenic steroids in almost quantitative yield. The whole synthetic route is summarized in the following chart:



a: R = =O; 1b: R =  , 2b-4b: R = 

Application of the Dakin reaction to steroidal estrogens is a new attempt. We found that factors affecting this reaction are numerous. Out of them the relative amount of hydrogen peroxide employed and the nature of the reaction medium in conjunction with its pH value are of prime importance. Failure to control these factors often results in the formation of intractable materials.

EXPERIMENTAL

Melting points were determined with a Zeiss microscopic hot stage apparatus and are uncorrected. Ultraviolet spectra were taken in anhydrous ethyl alcohol with an SP 8000 UV-spectrometer. Infrared spectra were taken in KBr using a P-E 588 B spectrometer. Nuclear magnetic resonance spectra were obtained at 100 MHz on a JEOL SP spectrometer, deuteriochloroform being employed as solvent. Chemical shifts are given in the δ (ppm) scale with tetramethylsilane as an internal standard. Mass spectrometry was performed on a JMS-D300 GC-MS/COM instrument.

2-Acetyl-3-hydroxyestra-1,3,5(10)-trien-17-one(3a). Chlorobenzene(80ml), acetyl chloride (2.2 ml), anhydrous aluminum chloride(6.0 g) and estrone (3.00 g) were mixed and stirred vigorously at 0° for 3 h., 15° for 1.5 h. and finally at 80-85° for 8.5 h. More aluminum chloride (1.5 g) was added and the reaction was continued at 80-85° for an additional hour. The reaction mixture was poured into cold hydrochloric acid (5%). The chlorobenzene layer was separated and the aqueous layer was extracted with portions of ethyl acetate. The extracts were washed with water until the wash was neutral, dried over anhydrous sodium sulfate and then distilled under reduced pressure. The residue was taken up with methanol, from which the product was crystallized (2.02 g). The mother liquor was chromatographed on silica gel with benzene-ethyl acetate (20:1, v/v) as eluent to give further 0.21 g, a total 2.23 g of product (64.4%) with mp 160-162°(lit 162-163°(14)), IR: 3475, 1270-1255 (OH chelated), 1740 (17-keto), 1645 (keto in o-hydroxyl acetophenone), 1620, 1572, 1495 (benzene ring), 875 cm^{-1} (single isolated H on the benzene). UVλmax: 218, 264, 338 nm. H^1-NMR (δ): 0.92(s,3H, CH_3), 2.56 (s,3H,$COCH_3$), 6.63 (s,1H,C_4-H), 7.54 (s,1H, C_1-H), 11.95 (s,1H, chelated OH, eliminated on shaking with D_2O). Mass spectrum: M/e 312 (M^+). Anal: Calcd. for $C_{20}H_{24}O_3$ C 76.89; H 7.74, Found C 76.44; H 7.79.

2-Acetyl-estra-1,3,5(10)-triene-3,17β-diol 17-acetate(3b). A solution of acetyl chloride (4.0 ml) in chlorobenzene (15 ml) was added dropwise to a suspension of estradiol (2.40 g.) and aluminum chloride (10 g) in the same solvent (70 ml) at 0° under vigorous stirring. After stirring for 3 h. the mixture was stood at room temperature overnight and then allowed to react further at 20°,30° and 40°,at each temperature for 2 h.Work-up was the same as for 3a. Recrystallization from methanol gave the product 3b (1.20 g). The methanolic mother liquor was chromatographed to give a further 0.60 g, a total of 1.80 g of product (57.3%) with mp 195-197° (lit 195-197°(15)). IR: 3450, 1268-1240 (OH chelated), 1730, 1268-1240 (17-ester), 1646 (keto in o-hydroxy acetophenone) 1620, 1580, 1495 (benzene ring), 878cm^{-1} (single isolated H on benzene). UVλmax: 219, 265, 338nm. ^{1}H-NMR (δ): 0.80 (s,3H, CH_3), 2.00(s,3H, $OCOCH_3$), 2.48 (s,3H, $COCH_3$), 6.46 (s,1H, C_4-H), 7.38 (s,1H, C_1-H), 11.74 (s,1H, OH chelated, eliminated on shaking with D_2O). Mass spectrum: M/e 356(M^+). Anal: Calcd for $C_{22}H_{28}O_4$ C 74.13; H 7.92, Found C 74.23; H 7.57.

2,3-Dihydroxy estra-1,3,5(10)-trien-17-one(4a). To a solution of 2-acetyl estrone (0.468 g) in diglyme (10 ml), made alkaline with 1 N NaOH

(1.5 ml) was added 3% hydrogen peroxide (1.73 ml) at 12° and under a nitrogen atmosphere. More NaOH solution was added to maintain the pH of the solution within 8.2-8.5. After 5 h. the pH of the solution was brought to 4.0-3.5 with glacial acetic acid. Concentration at reduced pressure resulted in a solid residue which was taken up in 1,2-dichloroethane and chromatographed over silica gel. Elution with benzene-ether (10:4, v/v) and subsequent crystallization from benzene afforded the product 4a (0.399 g, 93.1%) with mp 191-193°(lit 191-193° (8)). IR: 3500-3300, 1275(OH), 1740 (17-keto), 1610, 1520, 1455 (benzene ring), 880cm^{-1}(single isolated H on benzene). UVλ max: 289nm. ^{1}H-NMR (δ):0.84 (s, 3H, CH_3), 5.70 (s, 2H, 2OH,eliminated on shaking with D_2O), 6.55, 6.75 (s, 2H, C_1-H and C_4-H). Mass spectrum: M/e 286 (M^+). Anal:Calcd for $C_{18}H_{22}O_3$ C 75.50; H 7.75, Found C 75.48; H 7.80.

Estra-1,3,5(10)-triene-2,3,17β-triol-17-acetate(4b). To a solution of 2-acetyl estradiol 17-acetate (0.261 g) in diglyme (20 ml) were added alternate portions of 1 N NaOH solution (1.2 ml) and 6% hydrogen peroxide (0.65 ml), pH being maintained within 8.2-8.5. After the reaction had proceeded for 30 h., the mixture was worked up as for 4a to afford product 4b (0.206 g, 85.2%) with mp 100-105°, resolidified, and melted at 180-181° (lit 100-109°, and 182-185°(2)). IR:3500-3200, 1270 (OH), 1740, 1700, 1270-1230 (17-ester), 1612,1520,1452(benzene ring), 882 cm^{-1}(single isolated H on benzene). UVλmax, 289 nm, ^{1}H-NMR (δ):0.80 (s, 3H, CH_3), 2.06(s, 3H, $OCOCH_3$), 5.82, 6.56(s, 2H, 2OH, eliminated on shaking with D_2O), 6.56, 6.76 (s, 2H, C_1-H and C_4-H). Mass spectrum, m/e:330 (M^+). Anal: Calcd for $C_{20}H_{26}O_4$ C 72.70; H 7.93, Found C 72.22; H 7.41.

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REFERENCES

1. Gelbke, H. P., Ball, P. and Knuppen, R., Adv. in Steroidbiochemistry and Pharmacology, 6, 81 (1977).
2. Fishman, J.,Tomasz, M. and Lehman, R.,J. Org. Chem., 25, 585 (1960).
3. Rao, P. N. and Axelrod, L. R., Tetrahedron, 10, 144 (1960).
4. Wheeler, O. H. and Montalvo, R., Science, 150, 493 (1965).
5. Nambara, T.,Honma, S. and Akiyama, S., Chem.Pharm.Bull., 18, 474(1970).
6. Gelbke, H. P., Haupt, O. and Knuppen, R., Steroids, 21, 205 (1973).
7. Gelbke,H.P., Ball,P., Haupt,O. and Knuppen,R., Steroids, 22,151(1973).
8. Michiya,K., Itsuo,Y. and Mihoko,T., Japan, Kokai, 74 100,070 (1974).
9. Ei, K.-H.,Zhao, H.-M., et al, Kexue Tongbao, 22, 536 (1977).
10. Li, J.-T., Zhao, H.-M., et al, Kexue Tongbao, 22, 539 (1977).
11. Rao, P. N. and Burdett,J. E., Jr., Synthesis (3) 168 (1977).
12. Stubenrauch, C. and Knuppen, R., Steroids, 28, 733 (1976).
13. Kanojia, R. M., Steroids, 30, 343 (1977).
14. Hoehn, W. M., US 2,846,453 (1958).
15. Crabbé, P., Maldonado, L.A. and Sanchez, I., Tetrahedron, 27,711(1971).

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