Regiospecific Syntheses of Modified Steroid Hormones. Part IV.[1b] 4-Bromo-oestrone and -17β-oestradiol

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Dehydrative aromatization of 4-bromo-10β-hydroxyoestr-4-ene-3,17-dione (3a), obtained regiospecifically from 4β,5β-epoxy-10β-hydroxyoestrane-3,17-dione (1) by α-mode oxiran opening to 4-bromo-oestrone (5), was accomplished by treatment with trifluoroacetic anhydride in dioxan at ambient temperature. The stability of the 17β-hydroxy-group to trifluoroacetic anhydride was established, and the synthesis of 4-bromo-17β-oestradiol (6) by the analogous 19-norsteroid route was accomplished.

MONOFLUORO-RING-A aromatic steroids, synthesized *via* 19-norsteroid intermediates, are described in the preceding papers.[1] A variant (see Scheme) of the regiospecific 19-norsteroid route to 2-fluoro-oestrone [1b] was designed to synthesize 4-bromo-oestrone (5) and 4-bromo-17β-oestradiol (6). The key intermediate, 4-bromo-10β-hydroxyoestr-4-ene-3,17-dione (3a), was prepared by regiospecific α-mode oxiran opening [2b] of 4β,5β-epoxy-10β-hydroxyoestrane-3,17-dione (1) [1b] with hydrobromic acid in acetone. The u.v. spectrum of intermediate (3a) [$\lambda_{max.}$ 257 nm (ε 13,300)] was consistent with the γ-hydroxy-α-bromo-αβ-enone structure (3a). A suitably mild dehydration reagent was sought that would permit dehydrative aromatization of the intermediate (3a) without loss or rearrangement of the 4-bromo-substituent. Reagents such as thionyl chloride,[1b] phosphoryl chloride, and acids were avoided, as was the method of ester pyrolysis. Trifluoroacetic anhydride was considered a promising reagent, on the expectation that elimination of trifluoroacetate from the initial product 4-bromo-10β-trifluoroacetoxyoestr-4-ene-3,17-dione (3b) would occur with relative ease, with concomitant aromatization of ring A.† Indeed, such a reaction of compound (3a) in dioxan at 23° yielded 4-bromo-oestrone (5) in 64% yield. The n.m.r. spectrum of the product (5) exhibited two doublets, with splittings of 8·8 Hz, at δ 6·94 and 7·27 p.p.m., assigned to 2-H and 1-H, respectively, by analogy with shifts in the n.m.r. spectrum of 4-fluoro-17β-oestradiol diacetate.[1a]

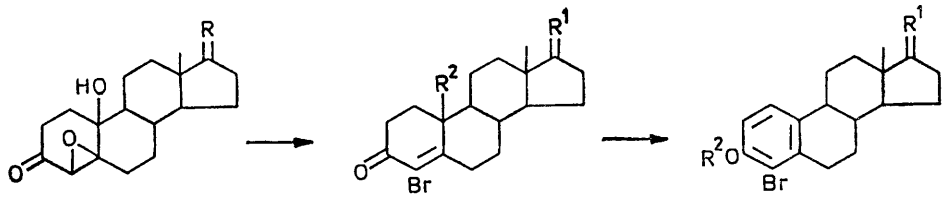
† An example of the elimination of trifluoroacetate, albeit under conditions considered excessively vigorous, is the conversion of 11β,17β,21-trihydroxy-5α-pregnane-3,20-dione 21-acetate 11β-trifluoroacetate into the corresponding 9(11)-ene, in a polar solvent (dimethylacetamide) at *elevated* temperature, 153°.[3]

[1] (*a*) Part II, M. Neeman, Y. Osawa, and T. Mukai, *J.C.S. Perkin I*, 1972, 2297; (*b*) Part III, M. Neeman, T. Mukai, J. S. O'Grodnick, and A. L. Rendall, preceding paper.

[2] (*a*) M. Neeman and J. S. O'Grodnick, *Tetrahedron Letters*, 1971, 4847; (*b*) 1972, 783.

[3] J. Elks and G. H. Phillips, *J. Chem. Soc.*, 1961, 4573.

A model experiment with oestradiol demonstrated the stability of the 17β-hydroxy-group on treatment with trifluoroacetic anhydride; hence 4-bromo-10β,17β-dihydroxyoestr-4-en-3-one (4a) was chosen as the key intermediate in the synthesis of 4-bromo-17β-oestradiol (6). Epoxidation of 10β,17β-dihydroxyoestr-4-en-3-one [4] with alkaline hydrogen peroxide gave, as expected,[1b] the β-epoxide (2) [δ 3·06 p.p.m. (4α-H)].[1b] Application of the α-mode oxiran opening reaction [2b] with hydrobromic acid to the epoxy-ketone (2) afforded 4-bromo-10β,17β-dihydroxyoestr-4-en-3-one (4a). Treatment of



(1) R = O
(2) R = α-H, β-OH

(3) a; R^1 = O, R^2 = OH
b; R^1 = O, R^2 = O·COCF$_3$
(4) a; R^1 = α-H, β-OH, R^2 = OH
b; R^1 = α-H, β-OH, R^2 = H

(5) R^1 = O, R^2 = H
(6) R^1 = α-H, β-OH, R^2 = H
(7) R^1 = α-H, β-OAc, R^2 = Ac

SCHEME

compound (4a) with trifluoroacetic anhydride in dioxan at ambient temperature yielded 4-bromo-17β-oestradiol (6) in 47% yield, identical with a specimen prepared by reduction of 4-bromo-oestrone (5) with sodium borohydride.

The regiospecific syntheses of 4-bromo-oestrone (5) and 4-bromo-17β-oestradiol (6) served to settle some long-standing differences in the characterizations of monobromo-ring-A aromatic steroids.[5-7] Utne and his co-workers [7] have summarized the inconsistencies between the characterizations of 4-bromo-oestrone (5) reported by Slaunwhite and Neely [5] and by Schwenk and his co-workers,[6] as well as between those of 4-bromo-17β-oestradiol (6) and of its diacetate (7), reported by Slaunwhite and Neely [5] and by Utne and his co-workers.[7] The characterization of 4-bromo-oestrone (5) in the present paper is in agreement with that of Schwenk and his co-workers,[6] and the characterizations of 4-bromo-oestradiol (6) and its diacetate (7) are identical with those of Utne and his co-workers,[7] thus confirming the latter by independent syntheses.

EXPERIMENTAL

For general directions see Part III.[1b]

4-Bromo-10β-hydroxyoestr-4-ene-3,17-dione (3a).—4β,5β-epoxy-10β-hydroxyoestrane-3,17-dione (1) [1b] (0·850 g) in acetone (34 ml) at 23° was treated with aqueous hydrobromic acid (48%; 1·1 ml) [2b] for 15 min. The mixture was then poured into ice–water (250 ml), and the precipitate was filtered off to yield *crystals* (3a) (0·533 g, 52%), $\lambda_{max.}$ (EtOH) 257 nm (ε 13,300), $\nu_{max.}$ (KBr) 1730 [C(17)=O] and 1690 [C(3)=O] cm^{-1}, δ(CDCl$_3$) 0·93 p.p.m. (3H, s, 18-H$_3$), (Found: C, 58·5; H, 6·4; Br, 22·0. $C_{18}H_{23}BrO_3$ requires C, 58·85; H, 6·3; Br, 21·75%).

The filtrate was extracted with ethyl acetate; the combined extracts were washed with water, dried (Na$_2$SO$_4$), and evaporated to yield a white solid (0·358 g, 29% by u.v.), identical (i.r. spectrum) with the precipitated product (total yield calculated on the basis of u.v., 81%).

4-Bromo-oestrone (5).—To a stirred solution of 4-bromo-10β-hydroxyoestr-4-ene-3,17-dione (3a) (0·505 g) in dioxan (15 ml), trifluoroacetic anhydride (10·8 ml) was added at 23°. After 64 h * at 23° the mixture was poured into ice–water (150 ml), neutralized with 2N-sodium hydroxide, and extracted with ethyl acetate. The combined extracts were washed with water, dried (Na$_2$SO$_4$), and evaporated to dryness to yield 4-bromo-oestrone (5) (0·573 g, 63% based on u.v.), $\lambda_{max.}$ (EtOH) 280 nm (ε 1260) and 286sh nm.

The product (5) (0·333 g) was placed on a column (2 × 62 in) of dry column adsorbent (640 g),[8] which was developed with benzene–ethyl acetate–ethanol (80 : 20 : 1) and cut into fractions,† and the steroid was removed from the silica gel with ethyl acetate. The fraction R_F 0·48—0·82 yielded 4-bromo-oestrone (5) (0·170 g, 62%), $\lambda_{max.}$ (EtOH) 282 (ε 2400) and 288 nm (2300), which formed white platelets, m.p. 280—281° (from chloroform–methanol) (lit.,[6] 281—283°; lit.,[5] 264—265°), $\lambda_{max.}$ (EtOH) 282 (ε 2380) and 288 nm (2300) [lit.,[6] 282 (ε 2234) and 299 nm (2340); lit.,[5] 281 nm (2170)], $\lambda_{max.}$ (EtOH–NaOH) 303 nm (ε 4040), $\nu_{max.}$ (KBr) 3417 (OH), 1731 [C(17)=O], 1590 and 1474 (aromatic C–H), and 817 (1,2,3,4-tetra-substituted benzene) cm^{-1}, $[\alpha]_D^{22}$ +134° (*c* 0·7 in CHCl$_3$), (lit.,[6] +147°; lit.,[5] +136°).

During one run, a sample was taken after 16 h at 23° and poured into water; filtration yielded white crystals (0·025 g), $\lambda_{max.}$ (EtOH) 257 nm (ε 7350), $\nu_{max.}$ (KBr) 1801 (trifluoroacetate C=O), 1741 [C(17)=O], 1697 [C(3)=O], and 1230 (trifluoroacetate C–O) cm^{-1}, regarded as 4-bromo-10β-trifluoroacetoxyoestr-4-ene-3,17-dione (3b). This material, when treated at 23° with trifluoroacetic anhydride in dioxan for 20 h, yielded 4-bromo-oestrone (5) (0·017 g), u.v. and i.r. spectra identical with those of authentic material.

* The time required for the completion of the reaction varied between 43 and 166 h.

† Compounds were located by u.v. illumination.

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[5] W. R. Slaunwhite, jun., and L. Neely, *J. Org. Chem.*, 1962, **27**, 1749.

[6] E. Schwenk, C. G. Castle, and E. Joachim. *J. Org. Chem.*, 1963, **28**, 136.

[7] T. Utne, R. B. Babson, and F. W. Landgraf, *J. Org. Chem.*, 1968, **33**, 1654.

[8] (*a*) B. Loev and M. M. Goodman, *Chem. and Ind.*, 1967, 2026; (*b*) B. Loev and K. M. Snader, *ibid.*, 1965, 15.

4β,5β-*Epoxy*-10β,17β-*dihydroxyoestran*-3-*one* (2).—To a stirred solution of 10β,17β-dihydroxyoestr-4-en-3-one [4] in methanol (60 ml) at 0° was added hydrogen peroxide (30%; 8·1 ml) followed by aqueous sodium hydroxide (16%; 2·9 ml). After 7 h at 0°, the mixture was poured into water, extracted with ethyl acetate, dried (Na_2SO_4), filtered, and evaporated. The total product (2) (1·241 g, 97%), which showed δ(Me_2CO) 3·06 p.p.m. (1H, s, 4-H), assigned to the 4α-oxiran proton, was crystallised from acetone–water to give the β-epoxide (2), m.p. 183—185°, $\nu_{max.}$ (KBr) 1690 [C(3)=O] cm^{-1}, δ(Me_2CO) 3·06 p.p.m. (1H, s, 4-H), c.d. (0·031M in dioxan) $\Delta\varepsilon_{312}$ +3·56 (with shoulders at 322 and 338 nm), o.r.d. (*c* 0·104 in dioxan) $[\Phi]_{700}$ + 427°, $[\Phi]_{589}$ + 522°, $[\Phi]_{339}$ + 8008°, $[\Phi]_{276}$ − 8265°, M^+, 306 (Calc. for $C_{18}H_{26}O_4$: *M*, 306).

4-*Bromo*-10β,17β-*dihydroxyoestr*-4-*en*-3-*one* (4a).—A solution of 4β,5β-epoxy-10β,17β-dihydroxyoestran-3-one (2) (0·306 g) in acetone (15 ml) was treated with aqueous hydrobromic acid (48%; 0·40 ml) for 40 min at 26°. The mixture was poured into water (75 ml) and extracted with ethyl acetate; the extract was dried (Na_2SO_4), filtered, and evaporated to yield the 4-*bromo-compound* (4a) (0·334 g, 77% based on u.v. data), m.p. 127—129° (from ethyl acetate–light petroleum), $\lambda_{max.}$ (EtOH) 258 nm (ε 10,790), $\nu_{max.}$ (KBr) 1681 (C=O) and 1575 (C=C) cm^{-1} (Found: C, 58·7; H, 6·75; Br, 21·55. $C_{18}H_{25}BrO_3$ requires C, 58·55; H, 6·8; Br, 21·65%).

Treatment of 17β-*Oestradiol with Trifluoroacetic Anhydride*.—To a solution of 17β-oestradiol (0·500 g) in dioxan (17 ml), trifluoroacetic anhydride (2·6 ml) was added. After 71 h at 23°, a sample (2·0 ml) was removed, poured into water (20 ml), and extracted with chloroform (3 × 20 ml); the extract was dried (Na_2SO_4) and the solvent removed to yield a solid, $\nu_{max.}$ ($CHCl_3$) 1795 (phenolic trifluoroacetate ester) and 1780 (17-trifluoroacetate ester) cm^{-1}. This product showed one spot, R_F 0·76, on t.l.c. (Eastman silica gel sheets, 80 : 20 : 1 benzene–ethyl acetate–ethanol); 17β-oestradiol showed one spot, R_F 0·48, in the same system. This product was assigned the 17β-oestradiol bistrifluoroacetate structure. The mixture was then heated to 40° for 11 h; a sample (2·0 ml) was removed and worked up as before to yield 17β-oestradiol bistrifluoroacetate, $\nu_{max.}$ ($CHCl_3$) 1795 and 1782 cm^{-1}, which showed one spot, R_F 0·75, on t.l.c. Hydrolysis gave 17β-oestradiol.

4-*Bromo*-17β-*oestradiol* (6).—To a stirred solution of 4-bromo-10β,17β-dihydroxyoestr-4-en-3-one (4a) (0·144 g) in dioxan (4·5 ml), trifluoroacetic anhydride (3·0 ml) was added. After 66 h the mixture was poured into water–ethanol (1 : 2; 40 ml), and sodium hydroxide was added (to pH 9). The solution was neutralized and extracted with ethyl acetate; the extract was evaporated and the residue (0·125 g) was placed on a nylon column (1 × 36 in) of silica gel adsorbent and eluted with benzene–ethyl acetate–ethanol (80 : 20 : 1). The fraction R_F 0·13—0·36 yielded 4-bromo-17β-oestradiol (6) (0·056 g, 47% based on u.v.); that of R_F 0·36—0·41 yielded starting material (4a) (0·009 g). Further similar dry column chromatography and two recrystallizations from methanol gave 4-bromo-17β-oestradiol as white needles (0·029 g), m.p. 214—215·5° (lit.,[7] 213·5—215°; lit.,[5] 207—208°), $\lambda_{max.}$ (EtOH) 282 (ε 2370) and 288 nm (2323), (lit.,[7] 283 and 288 nm; lit.,[5] 283 nm), $\lambda_{max.}$ (EtOH–NaOH) 303 nm, (ε 3790), $\nu_{max.}$ (KBr) 1607 and 1561 (aromatic C–H) cm^{-1} $[\alpha]_D^{21}$ +43·3° (*c* 0·24 in $CHCl_3$) (lit.,[7] +43°; lit.,[5] +129°). This material was identical (m.p., mixed m.p., u.v. and i.r. spectra, $[\alpha]_D$) with a specimen prepared by sodium borohydride reduction of 4-bromo-oestrone (5) and showed δ(Me_2SO) 7·19 (1H, d, *J* 8·8 Hz, 1-H) and 6·83 p.p.m. (1H, d, *J* 8·8 Hz, 2-H). 4-Bromo-17β-oestradiol diacetate (7) had m.p. 176—177° (lit.,[7] 175·5—177·5°; lit.,[5] 143—144°), $\lambda_{max.}$ (EtOH) 260 (ε 472), 268 (510), and 277 nm (396), (lit.,[7] 269 and 277 nm; lit.,[5] 275 nm), $\lambda_{max.}$ (EtOH–NaOH) 303 (ε 7160) and 244 nm (7000), $\nu_{max.}$ (KBr) 1769 (phenolic ester) and 1724 (17-ester) cm^{-1}, δ($CDCl_3$) 7·36 (1H, d, *J* 8·8 Hz, 1-H), 6·97 (1H, d, *J* 8·8 Hz, 2-H), 2·34 (3H, s, 3-OAc), and 2·06 p.p.m. (3H, s, 17-OAc), $[\alpha]_D^{22}$ +24° (*c* 0·21 in $CHCl_3$) (lit.,[7] +25°; lit.,[5] +103°).

We thank the American Cancer Society and the National Science Foundation for grants (to M. N.). We also thank the National Institutes of Health for pre-doctoral traineeships (to J. S. O. and K. M.) and the State of New York Health Department for a fellowship (to J. S. O.).

[2/850 *Received*, 17*th April*, 1972]