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A NEW TOTAL SYNTHESIS OF EQUILIN

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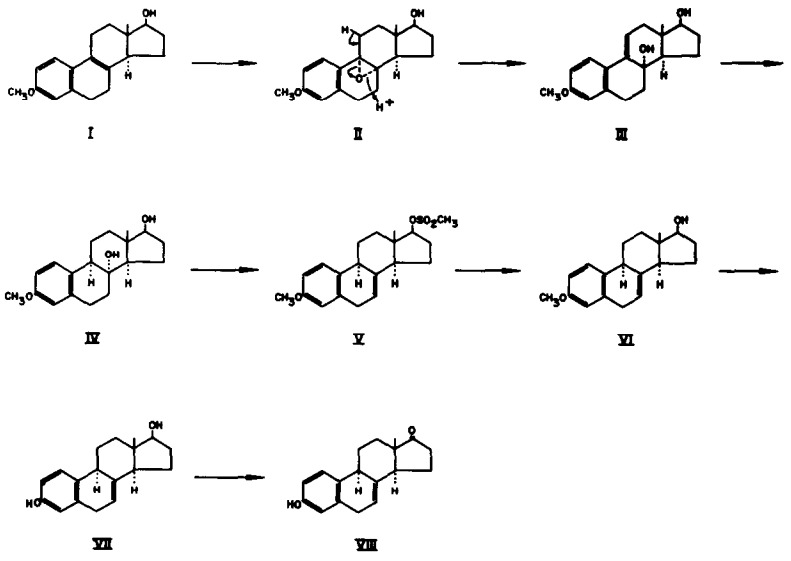
Equilin, a principal constituent of a clinically important natural estrogen preparation (1), has been synthesized by two previously published methods (2,3). Both used steroid starting material from natural sources, and the first (2), necessarily involving a final microbiological dehydrogenation, cannot, strictly, be considered a chemical total synthesis. We now report a further total synthesis of equilin which avoids relay steroids (4) of natural origin and introduces several novel steroid intermediates and reactions.

The estratetraene I (5), m.p. 129-131°, $[\alpha]_D$ -6° (c=3, $CHCl_3$) [lit. (5) m.p. 125°, $[\alpha]_D$ -3° (c=0.8, $CHCl_3$)], prepared by chemical resolution (6) of the corresponding racemate (7), on treatment at 0° with m-chloroperbenzoic acid in benzene-hexane, gives a mixture of the epoxide II and the diol III (8). Benzoic acid in chloroform converts the mixture to pure III (9), m.p. 131-133°, λ_{max}^{EtOH} 258 mμ (ε 17,600), $[\alpha]_D$ -22.3° (c=1, dioxan), which, on catalytic hydrogenation in ethanol over 5% palladized charcoal, gives the diol IV, m.p. 146-148°, λ_{max}^{EtOH} 220 (shoulder), 277 and 285 mμ (ε 8,400, 2,400 and 2,400), $[\alpha]_D$ +32° (c=1, dioxan). Methanesulfonyl chloride in refluxing pyridine converts IV to the tetraene sulfonate V, m.p. 160-163°, λ_{max}^{EtOH} 223 (shoulder), 277 and 286 mμ (ε 7,700, 4,100 and 3,200), (10) $[\alpha]_D$ +110° (c= 1, $CHCl_3$). The crude product is contaminated with ca. 10% of the 17-methanesulfonate of I, as estimated by the ultra-violet absorption spectrum, but

this is efficiently removed by filtration in benzene through Florex and recrystallization from methanol. Lithium aluminum hydride reduction of V in tetrahydrofuran gives VI, m.p. 80-82°, λ_{max}^{EtOH} 225 (shoulder), 277 and 286 mμ (ε 9,200, 4,500 and 3,700), $[\alpha]_D$ +168° (c=1, dioxan), which, on fusion with methylmagnesium iodide at 160° (bath) (11), gives the known diol VII (12), m.p. 206-208°, λ_{max}^{EtOH} 227 (shoulder), 277 and 286 mμ (ε 12,600, 3,700 and 2,800), $[\alpha]_D$ +190° (c=1, EtOH), [lit. (12) m.p. 205.5-206°; $[\alpha]_D$ +213° (c=1, EtOH)]. Aluminum isopropoxide and methyl ethyl ketone in refluxing benzene converts VII to equilin VIII, m.p. 234-237°, λ_{max}^{EtOH} 223 (shoulder) 279 and 286 mμ (ε 6,800, 2,500 and 1,650), $[\alpha]_D$ +295° (c=1, EtOH) [lit. (13), m.p. 240°, λ_{max} 280 mμ (ε 2,000) and $[\alpha]_D$ +308° (dioxan)]. This substance shows no depression with a sample of natural origin, and the infra-red absorption spectra of both are superimposable. Also, Oppenauer oxidation as before of the alcohol VI gives equilin methyl ether, m.p. 158-160°, $[\alpha]_D$ +266° (c=1, $CHCl_3$), which is identical with a sample, made by methylating authentic equilin (14) having m.p. 162-164°, $[\alpha]_D$ +295° (c=1, $CHCl_3$) [lit. (14) m.p. 161-163°, $[\alpha]_D$ +290° (c=1, $CHCl_3$)]. No systematic efforts have yet been made to improve the overall yield for the seven stages from I to VIII which presently stands at 16%, an average of 70-80% for each stage.



The epoxide II is formulated as an α-epoxide by analogy with the formation of 6α,7α-epoxy-3-methoxyestra-1,3,5(10)-trien-17β-ol from the corresponding estra-1,3,5(10),6-tetraene (15), and the diol IV as an 8α-ol from its proton NMR spectrum which shows a methyl singlet at a chemical shift of δ 0.83 ppm (16) closely similar in position to that found for 3-methoxy-8α-estra-1,3,5(10)-trien-17β-ol (δ 0.83 ppm), and appreciably different in position from that observed with 3-methoxyestra-1,3,5(10)-trien-17β-ol (δ 0.76 ppm). On this basis we express the mechanism for the formation of III as shown in II. Notably, only one hydrogen atom (the C_7 β-H) in structure IV is in the transdiaxial or pseudo-transdiaxial relationship with the C_8-α-hydroxyl, as compared to three (including the C_9-H) having this relation-

ship with the 8β-hydroxyl in the 8-epimer of IV. Possibly therefore the efficient formation of V from IV is associated with a kinetically controlled bimolecular elimination mechanism (17). A Dreiding model indicates the structure of III to be curved inwards at the β-face, which may explain its observed α-face catalytic hydrogenation. The foregoing aspects, and a number of variants of the synthesis now under investigation, will be discussed fully in a later communication.

Gibian et. al., (18) have recently reported a modification of one of our earlier syntheses (7), which, by using a microbiological asymmetric reduction, leads to the tetraene I without formation of unwanted enantiomorphic steroids. The basic starting material for these processes is 6-methoxy-1-tetralone; the present synthesis accordingly makes possible an efficient preparation of equilin from that substance.

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9. This and other single substances reported have given satisfactory elemental analyses.

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