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STEROIDS. X.[1] AROMATIZATION EXPERIMENTS IN THE CHOLESTEROL SERIES

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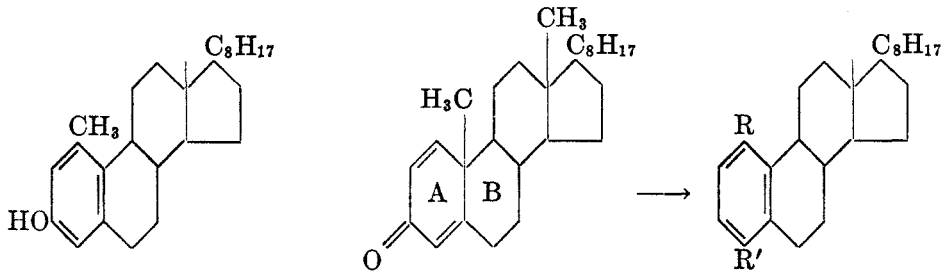
The preparation of sterols in which the hydroaromatic ring A with the angular methyl group at C-10 is replaced by a phenolic ring has been attempted several times. In 1936, Marker and co-workers (1) reported in a preliminary communication that dehydroneoergosterol afforded the phenol tetrahydrodehydroneoergosterol on reduction with sodium in amyl alcohol. The experimental details have never been reported and the claim could not be substantiated by other workers (2). In 1941, Inhoffen and Zühlsdorff (3) applied the acid-catalyzed dienone-phenol rearrangement to 1,4-cholestadien-3-one (I) and ascribed structure II to the resulting product. This would constitute the partial synthesis of an aromatic cholesterol analog with a methyl group in position 1, but the recent synthesis of 1-methyl-3-hydroxy-19-nor-1,3,5-cholestatriene (II) in this laboratory (4) clearly demonstrated that Inhoffen's product (3) belongs to the "x-methylheterophenol" series and most likely possesses structure III or IV (5). Earlier attempts to prepare the aromatic cholesterol analog (VII) *lacking* the methyl group at C-1 by thermal treatment of 1,4-cholestadien-3-one (I) failed (3, 6).

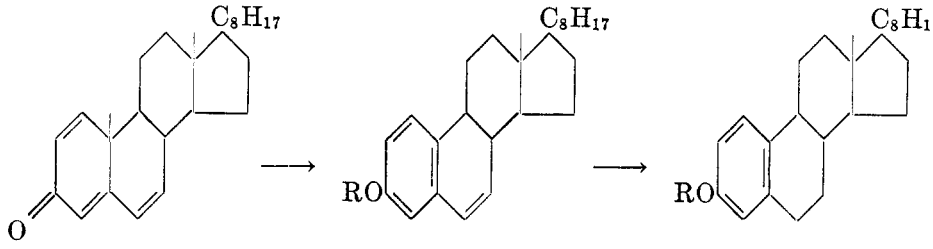


II I III R = CH_3; R′ = OH
IV R = OH; R′ = CH_3

It has recently been reported (7, 8) that vapor phase aromatization of 1,4,6-trien-3-ones of the androstane series leads to 6-dehydrophenols of the estrogen series, which can be hydrogenated to the natural estrogens in high yield. The present report deals with the application of this method to the first successful synthesis of a cholesterol derivative possessing an aromatic ring A and no methyl group at C-1.

Initial attempts to aromatize 1,4,6-cholestatrien-3-one (V) in mineral oil solution (7, 8, 9) failed because the resulting product was too soluble to crystallize from that medium. Substitution of tetralin (10) for mineral oil and a temperature of 670–700° proved to be satisfactory, since evaporation of the solvent left an

[1] For paper IX of this series, see Romo, Djerassi and Rosenkranz (4).



V

VIa R = H
b R = *p*-$NO_2C_6H_4CO$
c R = C_6H_5CO
d R = CH_3CO

VIIa R = H
b R = *p*-$NO_2C_6H_4CO$
c R = C_6H_5CO
d R = CH_3CO

oil, which readily yielded a crystalline *p*-nitrobenzoate (VIb). Saponification afforded the free phenol, 3-hydroxy-19-nor-1,3,5,6-cholestatetraene (VIa), and on esterification the benzoate (VIc) and acetate (VId). The negative rotation and ultraviolet absorption spectrum (main maximum at 266 mμ) are fully consistent with that formulation (4, 8). The phenol VIa smoothly absorbed one mole of hydrogen in the presence of 5% palladium-on-charcoal catalyst and led to the desired aromatic cholesterol analog, 3-hydroxy-19-nor-1,3,5-cholestatriene (VIIa), which was further characterized by three derivatives (VIIb, c, d). It is noteworthy that the corresponding derivatives in the tetraene (VI) and triene (VII) series possess nearly identical melting points but as observed already in the estrogen series (8), hydrogenation of the 6,7-double bond resulted in a large dextrorotatory shift of the specific rotation, and the ultraviolet absorption spectrum (maximum at 284 mμ and minimum at 250 mμ) was typical of that of a simple phenol. Just like the corresponding derivatives bearing a 1-methyl group (4), the presently described phenols (VIa and VIIa) were only very slightly soluble in 5% aqueous alkali and gave no color with alcoholic ferric chloride solution. Both phenols were rather sensitive to atmospheric oxidation.

EXPERIMENTAL[2]

3-Hydroxy-19-nor-1,3,5,6-cholestatetraene (VI). A solution of 40 g. of 1,4,6-cholestatrien-3-one (V) (4, 7, 8) in 3 l. of freshly distilled tetralin was dropped through a vertical glass tube (32 × 3.0 cm.) filled with Pyrex helices and heated to 670–700° over a period of 100 minutes. The condensate was concentrated to a small volume *in vacuo* and the remainder of the tetralin was removed by steam-distillation. Extraction of the residue with ether, drying, and evaporation left 34 g. of a brown oil, which was dissolved in 200 cc. of pyridine. After addition of 34 g. of *p*-nitrobenzoyl chloride, the mixture was briefly warmed on the steam-bath and then left at room temperature overnight. The *p*-nitrobenzoate (VIb) was isolated by dilution with water, extraction with chloroform, thorough washing with dilute hydrochloric acid and sodium carbonate solution, drying, concentration, and addition of methanol. The dark brown precipitate (25 g.) was dissolved in a mixture of 300 cc. of benzene and 100 cc. of hexane and filtered through a column of 300 g. of alumina. Evaporation

[2] All melting points are corrected and were determined on the Kofler block. Unless indicated otherwise, rotations were determined in chloroform solution and ultraviolet absorption spectra in 95% ethanol solution. We are greatly indebted to the Srtas. Paquita Revaque and Maria Eugenia Frontana for the rotations and spectra, and to Srta. Amparo Barba of our Microanalytical Department for the analyses.

of the solvent and two recrystallizations from a mixture of chloroform and methanol gave 13 g. (25%) of the *p-nitrobenzoate* VIb with m.p. 204–206°, $[\alpha]_D^{20}$ − 53.4°. Further recrystallization from methanol-ethyl acetate afforded the analytical sample with m.p. 218–220°, $[\alpha]_D^{20}$ − 53°, u.v. maximum at 264 mμ, log ε 4.37 (chloroform).

Anal. Calc'd for $C_{33}H_{41}NO_4$: C, 76.86; H, 8.01; N, 2.71.

Found: C, 77.00; H, 8.13; N, 2.95.

Three grams of the *p*-nitrobenzoate VIb was refluxed for 30 minutes with 200 cc. of methanol and 3 g. of potassium hydroxide, diluted with water, acidified, and extracted with ether. Evaporation of the solvent and trituration with hexane afforded 2 g. (93%) of the *phenol* VIa, m.p. 110–115°. The analytical sample crystallized from dilute methanol as colorless needles, turning yellow on heating, m.p. 121–123°, $[\alpha]_D^{20}$ − 59.2°, u.v. maxima at 224 mμ (log ε 4.49), 266 mμ (log ε 3.96), and 304 mμ (log ε 3.21).

Anal. Calc'd for $C_{26}H_{38}O$: C, 85.18; H, 10.44.

Found: C, 84.92; H, 10.55.

Benzoylation of 0.5 g. of the phenol VIa in pyridine solution with benzoyl chloride at room temperature overnight produced 0.52 g. of the *benzoate* VIc, which crystallized from methanol-ether in two polymorphic forms, m.p. 138–140° or m.p. 128–130°, $[\alpha]_D^{20}$ − 43.7°, u.v. maxima at 230 mμ (log ε 4.49) and 262 mμ (log ε 4.03).

Anal. Calc'd for $C_{33}H_{42}O_2$: C, 84.20; H, 8.99.

Found: C, 84.33; H, 9.24.

The *acetate* VId crystallized from methanol-ether as colorless plates with m.p. 96–98°, $[\alpha]_D^{20}$ − 42°, u.v. maxima at 226 mμ (log ε 4.50) and 264 mμ (log ε 4.09).

Anal. Calc'd for $C_{28}H_{40}O_2$: C, 82.30; H, 9.86.

Found: C, 82.22; H, 10.09.

3-Hydroxy-19-nor-1,3,5-cholestatriene (VII). An ethyl acetate solution of 5 g. of the tetraene VIa was shaken with 0.5 g. of 5% palladium-on-charcoal catalyst (American Platinum Works, Newark, N. J.) in an atmosphere of hydrogen for 45 minutes at which time the hydrogen up-take corresponded to one mole. Filtration, evaporation of the solvent to dryness, and recrystallization from methanol yielded 4.2 g. (83%) of the phenol VIIa as needles with m. p. 113–114°, $[\alpha]_D^{20}$ ++74.9°, u.v. maximum at 284 mμ (log ε 3.20) and minimum at 250 mμ (log ε 2.30).

Anal. Calc'd for $C_{26}H_{40}O$: C, 84.71; H, 10.93.

Found: C, 84.59; H, 11.10.

The following derivatives of the phenol VIIa were prepared:

p-Nitrobenzoate VIIb (from ethyl acetate-methanol), m.p. 211–213°, $[\alpha]_D^{20}$ +56.4°.

Anal. Calc'd for $C_{33}H_{43}NO_4$: C, 76.56; H, 8.37.

Found: C, 76.67; H, 8.39.

Benzoate VIIc (from ether-methanol), small needles, m.p. 138–140°, $[\alpha]_D^{20}$ +50.5°.

Anal. Calc'd for $C_{33}H_{44}O_2$: C, 83.84; H, 9.38.

Found: C, 84.01; H, 9.34.

Acetate VIId (from ether-methanol), m.p. 93.5–95°, $[\alpha]_D^{20}$ +62°, u.v. maximum at 265 mμ (log ε 2.63) and minimum at 252 mμ (log ε 2.53).

Anal. Calc'd for $C_{28}H_{42}O_2$: C, 81.89; H, 10.30.

Found: C, 81.98; H, 10.15.

SUMMARY

Aromatization of a tetralin solution of 1,4,6-cholestatrien-3-one (V) at 700° produced 3-hydroxy-19-nor-1,3,5,6-cholestatetraene (VI), which on hydrogenation led to the phenol VII, an analog of cholesterol possessing an aromatic ring A. Both phenols were characterized by a number of derivatives.

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