[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF WISCONSIN]

18,19-BIS-NOR-D-HOMOTESTOSTERONE

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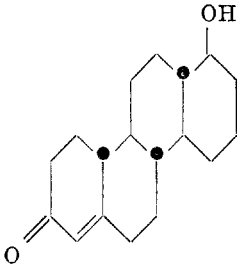
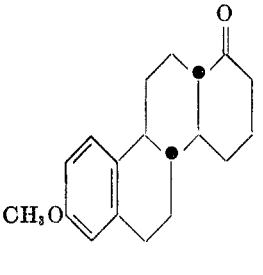
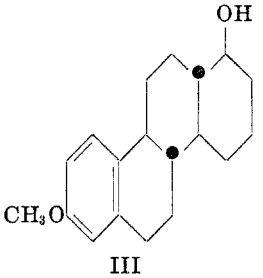
The 19-nor steroidal hormones that have been reported all exhibit significant and in some cases extraordinary physiological activity (1–4). This fact, coupled with the relatively high activity of 18-nor-D-homoandrostanedione (5) has prompted us to effect an even further simplification of the steroid molecule by eliminating both of the angular methyl groups. Birch and Quartey (6) have recently made a preliminary announcement of the synthesis of a nonhomogeneous specimen (presumably a mixture of stereoisomers) having the 11-hydroxy-18,19-bisnor-D-homotestosterone structure. The crude product exhibited "weak, but definite androgenic activity." In the present work we are reporting the synthesis of what we feel is authentic (stereochemically as well as structurally) *dl*-18,19-bisnor-D-homotestosterone (I).



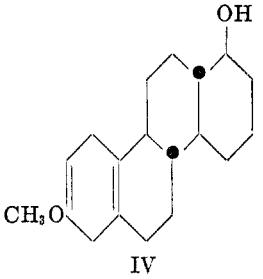
I



II



III



IV

In a previous study relating to the total synthesis of estrone (7) the acetylenic carbinol arising from the mole for mole condensation of *m*-methoxyphenylacetylene and 1,5-decalindione, was hydrogenated, dehydrated, and cyclized with aluminum chloride to yield a mixture from which two stereoisomeric ketomethoxydodecahydrochrysenes were isolated. That form (the "β isomer") melting at 155° must have the natural configuration indicated by formula II,

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since it was convertible into estrone. The carbinol III produced on lithium aluminum hydride reduction of II, (7) most probably has the C_{17_a} hydroxyl oriented in the β-configuration, because it can thus assume the thermodynamically more stable equatorial conformation (8). By analogy to the method of formation of 19-nortestosterone from ethers of estradiol (1, 4), the carbinol III was, in the present work, reduced by the Wilds-Nelson (4) modification of the Birch reduction (1). Thus when a solution of III in ammonia was treated with lithium followed by alcohol, it was readily converted to the enol ether IV. Acid hydrolysis of IV effected cleavage of the enol ether linkage and isomerization of the ethylenic bond into conjugation with the keto group to give *dl*-18,19-bisnor-D-homotestosterone (I), m.p. 213°. That the bond is in conjugation with the keto group was shown by the absorption in the ultraviolet (λ_{max} 240.5 mμ, ϵ 17,000) which is identical with that of 19-nortestosterone (4). The assignment of the β-configuration for the C_{10} hydrogen atom in I follows by analogy to the case of 19-nortestosterone (1, 4, 9).

For preparative purposes, the ketone II could be treated directly by the lithium in ammonia-alcohol sequence and the crude product hydrolyzed with acid. The reaction has not been worked out for best yields, but in one experiment I was thus prepared directly without isolation of III or IV in 61% overall yield.

Preliminary tests in rats performed under the direction of Drs. R. K. Meyer and Elva G. Shipley of the Department of Zoology showed I to have no appreciable androgenic activity at a dose of 2.83 mg. compared with a strong response exhibited by 0.174 mg. of testosterone; however, at these levels the myotrophic response of I was approximately equivalent to that of testosterone. In view of these results it would not be surprising to find that I has androgenic activity at higher dose levels.

EXPERIMENTAL[3]

dl-1,4-Dihydro-3,17β-18-nor-D-homoestradiol 3-methyl ether (IV). The following procedures are based on those of Wilds and Nelson for the preparation of 19-nor-testosterone (4). A solution of 0.143 g. of the β-isomer of 1-hydroxy-8-methoxy-1,2,3,4,4a,4b,5,6,10b,-11,12,12a-dodecahydrochrysene (III) (7), m.p. 140–140.5°, in 11 ml. of anhydrous ether was placed in a 100-ml. flask fitted with a sealed stirrer and an addition neck capped with a calcium chloride drying tube. After the addition of 14 ml. of liquid ammonia, which caused the mixture to become cloudy, 0.145 g. of freshly cut lithium wire was added in about 6 pieces over a 5-minute period. The resulting dark blue mixture was stirred for 10 minutes during which time the ammonia lost by evaporation was replenished. Absolute ethanol (1.6 ml.) was then added dropwise over a 5-minute period, the frothing being controlled by stopping the stirrer occasionally. After the alcohol was all added stirring was continued without further addition of ammonia. The blue color disappeared after the first 10 minutes of stirring. After most of the ammonia had evaporated, 25 ml. of water was added followed by 25 ml. of ether. The ether layer was separated, washed three times with water, once with brine, and dried over sodium sulfate. On concentration of the ether there was obtained 0.070 g. of colorless needles, m.p. 148.5–150.5°, and 0.049 g., m.p. 139–145°. Recrystallization of the latter fraction from benzene gave 0.021 g., m.p. 149.5–150.5°. Repeated

[3] Melting points were taken on a micro-hot stage and are corrected for stem exposure.

recrystallization from benzene gave colorless needles, m.p. 151.5–153.5°, showing no appreciable absorption beyond 245 mμ.

Anal. Calc'd for $C_{19}H_{28}O_2$: C, 79.1, H, 9.79.
Found: C, 79.0; H, 9.80.

dl-18,19-Bis-nor-D-homotestosterone (I). (*a*) *From the enol ether* (IV). A solution of 0.0501 g. of crude enol ether IV (m.p. 140–144°) obtained from later crops in the preceding experiment in 2.5 ml. of methanol was warmed to 60°; then 1.5 ml. of 3% aqueous hydrochloric acid was added and the clear colorless solution was kept at 60° for 15 minutes. The colorless crystals obtained on cooling to room temperature were separated by centrifugation and washed twice with dilute methanol; yield 0.0186 g., m.p. 135–188°. Concentration of the mother liquor in a stream of nitrogen gave 0.0193 g. of purer material, m.p. 196–200°, as pale violet prisms. Treatment of the latter fraction with Norit in methanol solution, followed by two recrystallizations from benzene gave colorless needles, m.p. 211.5–213°. The m.p. was not depressed on admixture with the analytical specimen described below.

(*b*) *Directly from the β-isomer of 1-keto-8-methoxy-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysene* (II). Using the technique described above, 0.143 g. of the ketone II (7), m.p. 155.5–158.5°, in 11 ml. of anhydrous tetrahydrofuran was treated with 14 ml. of ammonia and 0.295 g. of lithium in eight portions. After stirring for 20 minutes, 3.2 ml. of absolute ethanol was added over a period of 3 minutes. It is noteworthy that there was no frothing at this point as compared with the case above in which ether was used. After the blue color disappeared (about 5 minutes), the ammonia was evaporated (bath temperature 50°), and 10 ml. of water was added, followed by 5 ml. of concentrated hydrochloric acid which caused the temperature of the homogeneous reaction mixture to rise to 60°. After standing for 15 minutes with no external heating, 10 ml. of water was added, and the mixture was extracted with chloroform. The chloroform extracts were washed with water, brine, and dried over potassium carbonate. Evaporation of the solvent in a stream of nitrogen left 0.147 g. of a tan, sticky crystalline residue, which showed no appreciable absorption in the 280 mμ region indicating essentially complete reduction of the anisole nucleus. The λ_{max} of 12,700 at 239 mμ corresponds to about 75% of I in this crude product. On washing this product with ether, 0.0846 g. (61% yield) of pale cream-colored crystals were obtained, m.p. 202–210°. Further recrystallizations from benzene (one Norit treatment) gave colorless needles, m.p. 211–213.5° (introduced at 204°), $\lambda_{max}^{95\%\ EtOH}$ 240.5 mμ (ε 17,000).

Anal. Calc'd for $C_{18}H_{26}O_2$: C, 78.8; H, 9.55.
Found: C, 78.6; H, 9.70.

SUMMARY

dl-18,19-Bis-nor-D-homotestosterone has been synthesized from *dl*-18-nor-D-homoestrone methyl ether by concomitant reduction of the keto group and the aromatic nucleus with lithium in ammonia and alcohol, followed by acid hydrolysis of the resulting enol ether. During hydrolysis the bond migrates into conjugation with the carbonyl group, probably leaving the molecule in the natural configuration. A preliminary report on the physiological action of this compound is given.

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REFERENCES

(1) BIRCH, *J. Chem. Soc.*, 367 (1950); *Ann. Repts. on Progr. Chem.* (*Chem. Soc. London*), **47**, 210 (1950).

(2) MIRAMONTES, ROSENKRANZ, AND DJERASSI, *J. Am. Chem. Soc.*, **73**, 3540 (1951).

(3) SANDOVAL, MIRAMONTES, ROSENKRANZ, DJERASSI AND SONDHEIMER, *J. Am. Chem. Soc.*, **75,** 4117 (1953).
(4) WILDS AND NELSON, *J. Am. Chem. Soc.*, **75,** 5366 (1953).
(5) JOHNSON, LEMAIRE, AND PAPPO, *J. Am. Chem. Soc.*, **75,** 4866 (1953).
(6) BIRCH AND QUARTEY, *Chemistry & Industry*, 489 (1953).
(7) JOHNSON, BANERJEE, SCHNEIDER, GUTSCHE, SHELBERG, AND CHINN, *J. Am. Chem. Soc.*, **74,** 2832 (1952).
(8) BARTON, *Experientia*, **6,** 316 (1950).
(9) KLYNE, *J. Chem. Soc.*, 2916 (1952).