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THE CONVERSION OF A STEROID TO 4',10-DIMETHYL-1,2-BENZANTHRACENE BY A MODEL OF A BIOCHEMICAL ROUTE

W.R. Nes and D.L. Ford

Department of Chemistry, Clark University, Worcester, Mass.

and

Worcester Foundation for Experimental Biology, Shrewsbury, Mass.

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THE suggestion[1] has been made that a carcinogenic derivative of a steroid might arise biochemically by the anthrasteroid rearrangement. We should now like to report the model preparation of 4',10-dimethyl-1,2-benzanthracene (X) from a steroid [pregnenolone (I) or ergosterol (II)] by successive anthrasteroid and D-homosteroid rearrangements followed by dehydrogenation. 1,2-Benzanthracenes substituted with a methyl group at C-10 are already known to be potent carcinogens.[2]

The formation of X from I demonstrates for the first time that an aromatic hydrocarbon of the 1,2-benzanthracene class can be derived from a steroid bearing only the C_2-hormonal side chain. Furthermore, the formation of X could conceivably proceed biologically, since the steps we have used parallel known types of biochemical reactions. Thus, (a) for the conversion of IV to VI we have used 17α-hydroxylation which is a well known function of the adrenal gland; (b) the D-homosteroid rearrangement which was carried out for the conversion of VI to VII has been observed in both

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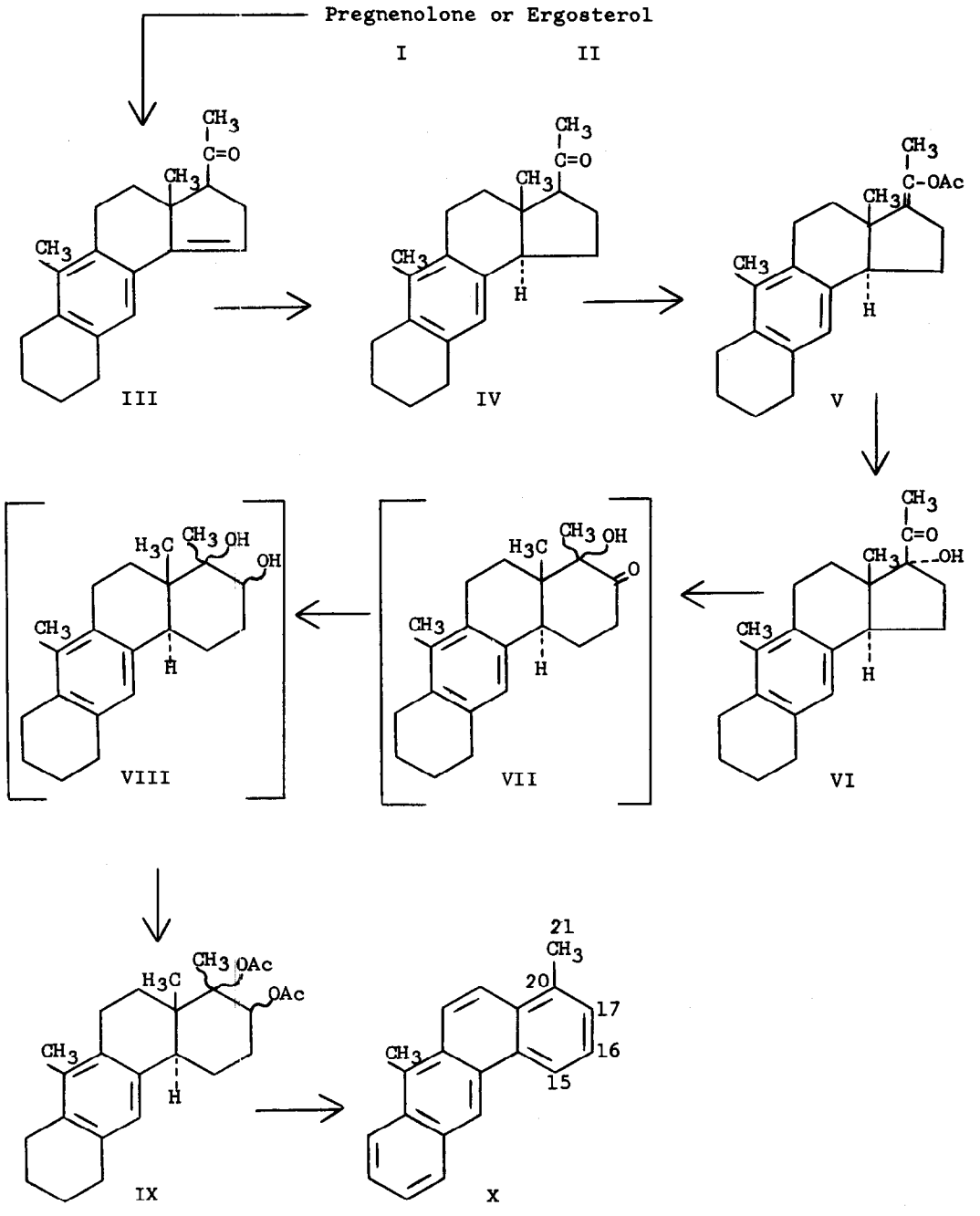
[1] W.R. Nes and E. Mosettig, J. Amer. Chem. Soc. 76, 3182 (1954).

[2] J.L. Hartwell, Survey of Compounds Which Have Been Tested For Carcinogenic Activity. U.S. Public Health Service Publication No. 149, pp. 152-157, 179-180. U.S. Government Printing Office, Washington (1951).


Pregnenolone or Ergosterol
I
II
III
IV
V
VI
VII
VIII
IX
X

microorganisms[3] and mares;[4] and (c) the removal of C-18 which we effected with palladium and heat could reasonably occur biochemically by the oxidation of C-18 to a carboxyl group (known in mammals[5]) followed by decarboxylation. Of the major conversions, only the anthrasteroid rearrangement itself has not yet been demonstrated biologically, but a modification of the closely similar dienone-phenol rearrangement has recently been documented in microorganisms.[6,7]

5,7,9,14-Anthrapregnatetraen-20-one (III), obtainable from either pregnenolone[8] or ergosterol,[9] was reduced (Pd/C, H_2) to 5,7,9-anthrapregnatrien-20-one [IV; 90%; from methanol, needles, m.p. 122-123°; $[\alpha]_D^{23}$ +87° ($CHCl_3$); $C_{21}H_{28}O$ (Found: C, 84.80; H, 9.56); $\lambda_{max}^{iso\text{-}octane}$ 273, 278 and 283 mμ (ε 650, 540 and 675); λ_{max}^{KBr} 5.88 μ] which was then converted to the enol acetate [V; 45%; from acetone, needles, m.p. 139-145°; the elemental analysis (Found: C, 82.20; H, 9.26) and the intensity of a weak absorption band at 5.87μ indicated 13% of starting material (IV) which was not separable by chromatography; λ_{max} 5.72 μ (strong)]. Treatment of V with OsO_4 followed by hydrolysis yielded 5,7,9-anthrapregnatrien-17α-ol-20-one [VI; 32%; from methyl cyclohexane, needles, m.p. 131-133°; $[\alpha]_D^{23}$ -63° ($CHCl_3$); $C_{21}H_{28}O_2$ (Found: C, 80.49; H, 9.35); λ_{max} 273, 277, 282 mμ (ε 706, 606, 766); $\lambda_{max}^{CS_2}$ 5.87 and 5.93 μ]. The hydroxy ketone (VI) was submitted to the D-homosteroid rearrangement (KOH/CH_3OH) and the product (VII) without

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[3] J. Fried, R.W. Thoma, J.R. Gerke, J.E. Herz, M.N. Donin and D. Perlman, J. Amer. Chem. Soc. 74, 3962 (1952).

[4] W. Klyne, Nature, Lond. 166, 559 (1950).

[5] R. Neher and A. Wettstein, Helv. Chim. Acta 39, 2062 (1956).

[6] R.M. Dodson and R.D. Muir, J. Amer. Chem. Soc. 83, 4627, 4631 (1961).

[7] K. Schubert, K-H. Bohme and C. Horhold, Z. Naturf. in press; cited in Z. Physiol. Chem. 325, 260 (1961).

[8] W.R. Nes, J.A. Steele and E. Mosettig, J. Amer. Chem. Soc. 80, 5230 (1958).

[9] W.R. Nes and D.L. Ford, J. Amer. Chem. Soc. 83, 4811 (1961).

purification was reduced ($LiAlH_4$) to VIII which was characterized as the diacetate, 17a-methyl-5,7,9-anthra-D-homoandrostatriene-17a,17-diol diacetate [IX; 44% from VI; from acetone, plates, m.p. 256-257° (sealed capillary); $[\alpha]_D^{21}$ +75° ($CHCl_3$); $C_{25}H_{34}O_4$ (Found: C, 75.43; H, 8.70; $\lambda_{max}^{iso\text{-}octane}$ 273, 277 and 282 mμ (ε 640, 525 and 640); λ_{max}^{KBr} 5.77 μ]. Upon dehydrogenation (Pd/C) IX smoothly yielded the known 4',10-dimethyl-1,2-benzanthracene [X; 37%; from ethanol, colorless polymorphic crystals (usually thick needles), m.p. 154-156°; lit.,[10] m.p. 154-154.5°; $C_{20}H_{16}$ (Found: C, 93.52; H, 6.40); $\lambda_{max}^{iso\text{-}octane}$ 224, 234, 259, 276, 286, 298, 323, 338, 354, 373 and 392 mμ (ε 39,800, 36,200, 36,700, 41,500, 84,000, 101,000, 5300, 8500, 10,900, 8100 and 600)].

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[10] B.M. Mikhailov and T.K. Kozminskaya, Zh. Obshch. Khim. 23, 1220 (1953).