

A NOVEL BENZENOID STEROID

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Naturally occurring benzenoid steroids, notably estrogens with phenolic ring A, have been widely investigated^{1a}. An isomer of estrone (I), isolated from equine pregnancy urine has been assigned structure II², an example of a benzenoid ring B, and the alkaloid, veratramine³ (III) exemplifies a C-nor-D-homosteroid with aromatic ring D. In addition, considerable work has been reported on the aromatization of non-benzenoid steroids by molecular rearrangement or by elimination of the C-19 methyl group. The dienone-phenol and dienol-benzene rearrangements lead to a variety of ring A benzenoid types^{1b}, the neosteroids^{1c} have a benzenoid ring B, and the "des-hydratation aromatisante"⁴ of 17-ethynylcarbinols gives D-benzenoid-D-homosteroids. This communication describes a molecular rearrangement leading to a ring C benzenoid steroid.

¹ L. F. Fieser and M. Fieser, "Steroids", (Reinhold, New York, 1959); a) Chapter 15, b) pp. 323-329, c) pp. 104-108.

² R. D. H. Heard and M. M. Hoffman, J. Biol. Chem. 135, 801 (1940); 138, 651 (1941).

³ O. Wintersteiner, "Festschrift Arthur Stoll" (Birkhauser, Basel, 1957) pp. 166-176.

⁴ M. Dvolaitzky, A. M. Giroud and J. Jacques, Bull. Soc. chim. France 62 (1963).

The action of bromine on 5-dihydroergosteryl acetate (IV) has been reported⁵ to yield a rather unstable tetrabromoergostenyl acetate, which yielded ergosteryl-D acetate (VI) on zinc debromination. On the basis of this behaviour and the nuclear magnetic resonance spectrum which exhibits no signal characteristic of a vinyl proton, we now formulate the tetrabromide as 7,11,22,23-tetrabromoergost-8-en-3 β -yl acetate (V) [C₃₀H₄₆O₂Br₄, m.p. 129-130°, [α]_D+ 260° in benzene⁶]. From the bromination of IV, we have also isolated an isomeric tetrabromide [C₃₀H₄₆O₂Br₄, m.p. 200-201°, [α]_D- 390°] which has the structure 7,8,22,23-tetrabromoergost-14-en-3 β -yl acetate (VII). Structure proof and further reactions of these tetrabromides will be reported separately.

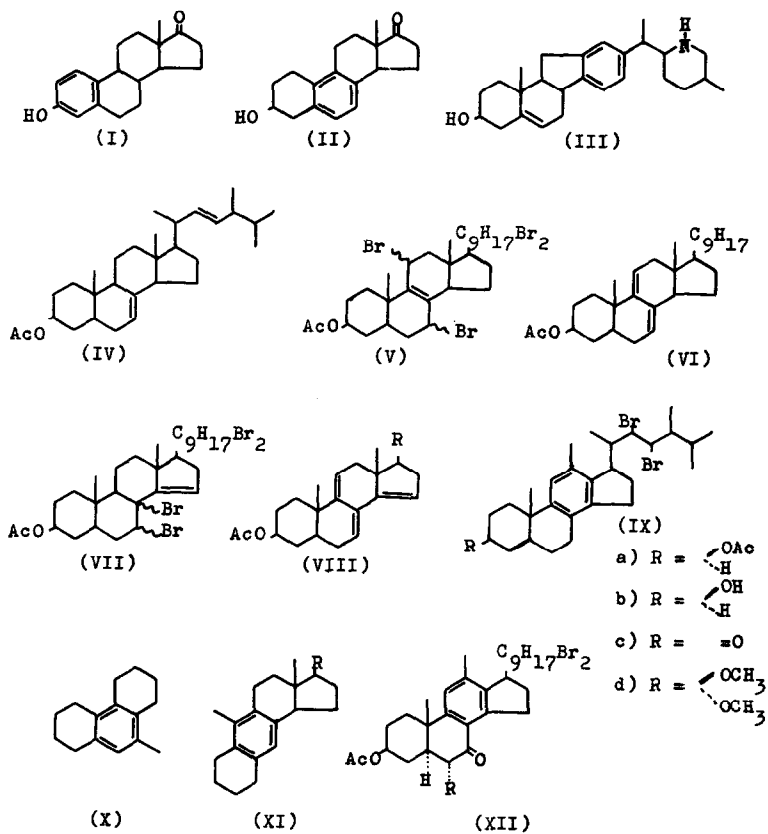
The instability of the tetrabromide (V) is exemplified by its behaviour on filtration of a benzene solution through chromatographic alumina; five crystalline products have been isolated, two in major amounts. The first, obtained in 60% yield using Merck acid-washed alumina (pH 3.75)⁷, was identified as 22,23-dibromoergosta-7,9(11),14-trien-3 β -yl acetate (VIII, R = C₉H₁₇Br₂) [C₃₀H₄₄O₂Br₂, m.p. 211-212°, [α]_D- 53°, λ 228(11,700), 234(11,000), 268 μ (10,000); maleic anhydride adduct, C₃₄H₄₆O₅Br₂, m.p. 226-227°, [α]_D+ 28°, λ 275 μ (4000)] by zinc debromination to the known ergosta-7,9(11),14,22-tetraen-3 β -yl acetate⁸

⁵ R. C. Anderson, R. Stevenson and F. S. Spring, J. Chem. Soc. 2901 (1952).

⁶ Unless specified to the contrary, specific rotations were determined in chloroform solution and ultraviolet absorption spectra in ethanol solution.

⁷ This value refers to the pH of a solution obtained by suspending the alumina (1.0 g.) in distilled water (10 ml.).

⁸ G. D. Laubach, E. C. Schreiber, E. J. Agnello and K. J. Brunings, J. Am. Chem. Soc. 78, 4746 (1956).



(VIII, R = C_9H_{17}) [$\text{C}_{30}\text{H}_{44}\text{O}_2$, m.p. 128-131°, $[\alpha]_D - 88^\circ$, $\lambda_{228}(10,000)$, $235(10,100)$, $268 \text{ m}\mu(9200)$].

The second major product, obtained in 90% yield with Woelm acid alumina (pH 3.75) or Spence Type H alumina (pH 9.10) is a benzenoid product for which we propose the structure, 22,23-dibromo-12-methyl-18-norergosta-8,11,13-trien-3 β -yl acetate (IXa) [$\text{C}_{30}\text{H}_{44}\text{O}_2\text{Br}_2$, m.p.

136-137°, $[\alpha]_D - 4^\circ$, $\lambda_{220\text{inf.}}$ (13,500), 261(247), 268(279), 277sh. μ (216) in iso-octane]. The ultraviolet absorption spectrum indicated a closer resemblance to the neo-steroids and 9-methyl-g-octahydro-phenanthrene (X) which have angular annulation than to a dihydroanthrasteroid⁹ (XI) which is linearly annulated or to veratramine (III)¹⁰. The tentative conclusion that the benzene ring is penta-substituted (strong infrared band at 866 cm^{-1} in CS_2 solution or KBr disk) was confirmed by the nuclear magnetic resonance spectrum¹¹ which has characteristic signals at τ 3.22 (aromatic proton, integrated intensity = one proton) and τ 7.78 (methyl group attached to benzene ring, integrated intensity = three protons). All derivatives gave ultraviolet, infrared and n.m.r. spectra consistent with this assignment.

Acid or alkaline hydrolysis yielded the corresponding alcohol (IXb) $[\text{C}_{28}\text{H}_{42}\text{OBr}_2]$, m.p. 111-113°, $[\alpha]_D + 5^\circ$ which on oxidation with the chromium trioxide-pyridine reagent yielded the ketone (IXc) $[\text{C}_{28}\text{H}_{40}\text{OBr}_2]$, m.p. 103.5°¹², $[\alpha]_D + 23^\circ$, $\lambda_{\text{KBr}} 5.83\mu$; 2,4-dinitrophenylhydrazone, $\text{C}_{34}\text{H}_{44}\text{O}_4\text{Br}_2\text{N}_4$, m.p. 227-228°, $\lambda_{367\text{m}\mu}$ (20,800) in CHCl_3]. Simple crystallization of the ketone from methanol afforded the dimethyl ketal (IXd) $[\text{C}_{30}\text{H}_{50}\text{O}_2\text{Br}_2]$, m.p. 138.5-140°, $[\alpha]_D + 14^\circ$, τ 6.87, 6.95 (two methoxyl groups)]. Bromination of the ketone (IXc) in acetic

⁹ I. Scheer, W. R. Nes and P. B. Smeltzer, *J. Am. Chem. Soc.* **77**, 3300 (1955).

¹⁰ W. A. Jacobs and L. C. Craig, *J. Biol. Chem.* **160**, 555 (1945).

¹¹ Nuclear magnetic resonance spectra were determined in CCl_4 solution with tetramethylsilane as an internal standard, using a Varian 4300B spectrometer at 60 mc.

¹² Obtained by crystallization from light petroleum or isopropyl ether, both tenaciously retained after extensive drying. The n.m.r. spectrum was measured on the pure sample, obtained as a glass by chromatography, and gave a total integrated intensity of 40 protons.

acid solution yielded a monobromoketone $[C_{28}H_{39}OBr_3]$, m.p. 184-184.5°, $[\alpha]_D^{25} + 40^\circ$, $\lambda_{KBr} 5.78\mu, 5.42(\text{multiplet})$. This observed n.m.r. multiplet splitting is characteristic of a methine proton at C-2 rather than C-4 and the infra-red carbonyl shift of $+15\text{ cm}^{-1}$ from IXc indicates that the bromine atom has an equatorial conformation as would be expected from its 1,3 relationship to an axial methyl group. The bromoketone, consequently regarded as the 2 α -bromo derivative of IXc, on treatment with 2,4-dinitrophenylhydrazine undergoes spontaneous elimination of hydrogen bromide to yield the dinitrophenylhydrazone of the Δ^1 -unsaturated-3-ketone $[C_{34}H_{42}O_4Br_2N_4]$, m.p. 223.5-224.5°, $\lambda_{382m\mu} (35,600)$ in $CHCl_3$. The ultraviolet absorption spectrum of this derivative is characteristic of α, β -unsaturated ketones¹³, establishing that ring A is not adjacent to the benzene ring and hence that ring B (intact or modified) is excluded as the site of the aromatic ring.

Oxidation of IXa with chromium trioxide in acetic acid solution gave a phenyl ketone, formulated as XII (R=H) $[C_{30}H_{42}O_3Br_2]$ ¹⁴, $\lambda 5.78, 5.98, 6.29\mu$ (in $CHCl_3$), $\lambda 219(23,800), 266(12,000), 311m\mu(2,600)$ and which yields the bromoketone XII (R=Br) $[C_{30}H_{41}O_3Br_3]$, m.p. 201-202°, $[\alpha]_D^{25} - 23^\circ$, $\lambda 5.78, 5.94, 6.27\mu$ (in $CHCl_3$), $\lambda 220(20,100), 274(12,000), 306sh. m\mu(3,100)$. The n.m.r. spectrum [doublet centered at $\tau 5.63$ ($J=14\text{ c.p.s.}$)] indicates that the proton at C-6 is axial and adjacent to an axial methine proton, and that the bromine atom consequently

¹³ C. Djerassi and F. Ryan, *J. Am. Chem. Soc.* **71**, 1000 (1949).

¹⁴ In its readily obtained pure form, this compound has not been obtained crystalline. It forms a co-crystal, m.p. 135-138°, $[\alpha]_D - 10^\circ$, with IXa.

has an equatorial (α) conformation¹⁵. This conclusion also supports the proposed structure (IXa) for the new benzenoid steroid. Satisfactory analyses have been obtained for all crystalline compounds.

No evidence is here presented excluding sidechain migration¹⁶ (e.g. to C-15) or configuration inversion during this molecular rearrangement, the generality of which is being examined.

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¹⁵ F. J. Schmitz and W. S. Johnson, Tetrahedron Letters, 647 (1962).

¹⁶ Considered unlikely since a 4-membered spiran would be involved [cf. S. Bloom, J. Am. Chem. Soc. 80, 6280 (1958)].