[CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH

The Structure of Inhoffen's Phenolic Steroids. I. Dehydrogenation[1,2]

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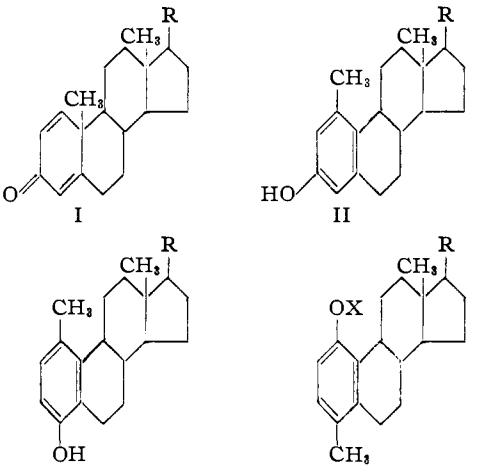
1,4-Androstadiene-3,17-dione was aromatized in acetic anhydride and acetic acid with zinc chloride as a catalyst. Saponification of the product yielded the 17-keto member of Inhoffen's *x*-methylheterophenols. Its methyl ether was subjected to a palladium degradation at 300° to give 1-methoxy-4-methyl-3-desoxyisoequilenin (VIII), 4-methyl-3-desoxyisoequilenin (IX), 1-ethyl-2,8-dimethylphenanthrene (X) and 1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (XI). The identification of the latter two compounds is confirmatory evidence that Inhoffen's phenolic steroids have the hydroxyl group attached at carbon-1 and the methyl group at carbon-4 and that they are, therefore, best represented by structure IV.

Inhoffen's pioneering work on the partial aromatization[3] of steroidal 1,4-diene-3-ones (I) has stimulated considerable interest in the nature of the reactions and of the products. The acid-catalyzed reaction, later known as the dienone–phenol rearrangement, was usually performed by Inhoffen in an acetic anhydride solution with concentrated sulfuric acid as a catalyst. Under these conditions a single phenolic product was formed in each case. By analogy with santonin[4] and with a model compound in the chrysene series,[5] it was thought that the aromatization proceeded with a migration of the methyl group (C-19) from the angular position to carbon-1, and that the products belonged to the class of 1-methyl-3-hydroxysteroids (II).

Later, Woodward and Singh,[6] on the basis of a carefully chosen model reaction, suggested two other structures, III and IV. This received confirmation when the real 1-methyl-3-hydroxysteroids (II), prepared by another method, were found to be clearly different from Inhoffen's corresponding phenolic compounds.[7] In view of their uncertain structure, the latter were named *x*-methylheterophenols.

In recent papers[8,9] Inhoffen and Woodward presented evidence for structure IV for these compounds. This was based on the selenium dehydrogenation of the *x*-methylheterophenol in the cholesterol series, which afforded the 8-methyl derivative of Diels hydrocarbon in small yield.[10]

In confirmation of Woodward and Inhoffen's conclusion, the present work offers independent evident for the 1-position of the hydroxyl group and the 4-position of the methyl group in Inhoffen's phenolic steroids. This was obtained from the palladium degradation of the 17-keto member of the series (V). This ketone (V) was first synthesized from I (R = O) by Djerassi and Scholz[11] by a modification of Inhoffen's procedure which made use of *p*-toluenesulfonic acid as a catalyst instead of sulfuric acid (the latter produced a side reaction) and thus necessitated a higher reaction temperature. It has now been found that 1,4-androstadiene-3,17-dione (I, R = O) readily rearranged at room temperature in an acetic anhydride–acetic acid medium with a trace of zinc chloride as a catalyst to give VI, which could not previously be obtained crystalline. Saponification yielded the same phenol (V) as had been obtained by Djerassi and Scholz.



The methyl ether VII was heated with 5% palladium-on-charcoal according to the procedure described[12] for steroids in the estrane series. Treatment at 300° for 20 minutes yielded four products, separable by chromatography and by fractional crystallization of the *sym*-trinitrobenzene derivatives. The main product (25% yield) was in all probability 1-methoxy-4-methyl-3-desoxyisoequilenin (VIII, the assignment of this structure will be justified below) with an ultraviolet absorption spectrum similar to that of 8-methoxy-5-methyl-1-naphthylethyl alcohol.[13] This spectrum shows the characteristic set of three broad peaks in the 290–340 mμ region, which are usually the only maxima found above 260 mμ in alkyl derivatives of α-naphthol (and their methyl ethers). Similar

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(2) A part of this work was supported by a Research and Development Contract between the Detroit Institute of Cancer Research and the United States Atomic Energy Commission. Additional support was provided by institutional grants from the Michigan Cancer Foundation, the American Cancer Society, Inc., and The Kresge Foundation.

(3) H. H. Inhoffen, *Angew. Chem.*, **53**, 471 (1940); **59A**, 207 (1947).

(4) A. Andreocci, *Gazz. chim. ital.*, **23**, II, 469 (1893); G. R. Clemo, R. D. Haworth and E. Walton, *J. Chem. Soc.*, 2368 (1929); Huang-Minlon, Chien-Pen Lo and L. Ju-Yung Chu, THIS JOURNAL, **65**, 1780 (1943).

(5) A. L. Wilds and C. Djerassi, *ibid.*, **68**, 1712, 1715, 2125 (1946).

(6) R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950).

(7) C. Djerassi, G. Rosenkranz, J. Romo, J. Patakai and St. Kaufmann, *ibid.*, **72**, 4540 (1950).

(8) H. H. Inhoffen, *Angew. Chem.*, **63**, 297 (1951).

(9) R. B. Woodward, H. H. Inhoffen, H. O. Larson and K. Menzel, *Ber.*, **86**, 594 (1953).

(10) H. H. Inhoffen, G. Stoeck and G. Kolling, *Ber.*, **82**, 263 (1949).

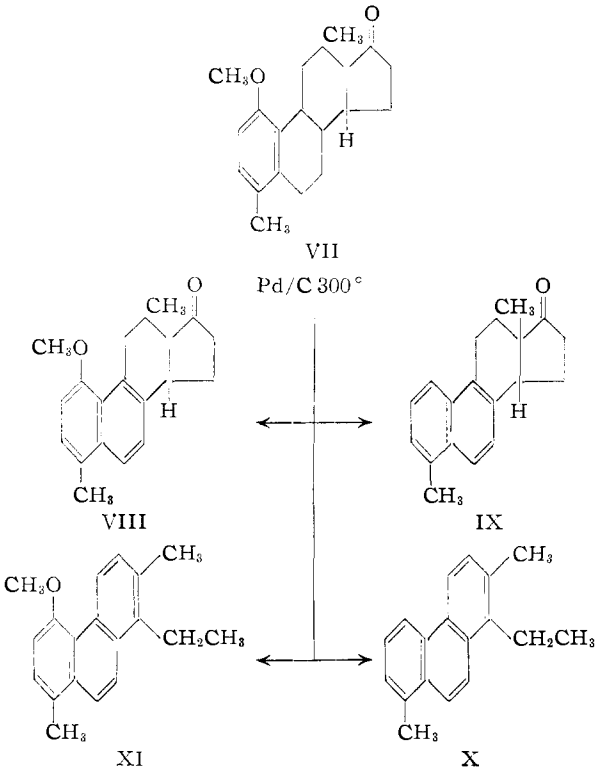
(11) C. Djerassi and C. Scholz, *J. Org. Chem.*, **13**, 705 (1948).

(12) W. E. Bachmann and A. S. Dreiding, THIS JOURNAL, **72**, 1323 (1950).

(13) A. S. Dreiding and A. J. Tomasewski, *ibid.*, **76**, 540 (1954).

derivatives of β-naphthol show two distinct sets of peaks in this region, one at 260–290 mμ and the other at 300–340 mμ.[14] The assumption that the dehydrogenation of the B-ring was accompanied by an epimerization at carbon-14, is based on analogy with the previously reported cases.[12]

A small amount (3%) of a second naphthalenoid steroid, probably 4-methyl-3-desoxyisoequilenin (IX), was also isolated. Its ultraviolet absorption spectrum was almost identical with that of 1,5,6-trimethylnaphthalene.[15]



Of greater interest were the other two degradation products in which a cleavage of ring D had taken place. These phenanthrene derivatives have been definitely identified by synthesis[13] as 1-ethyl-2,8-dimethylphenanthrene (X, 13% yield) and 1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (XI, 10% yield).[16] Since the ethyl group and one methyl group originated from the D ring of the steroid (VII),[12] they must be attached at the 1- and 2-positions. This leaves the 8-methyl group (in X and XI) and the 5-methoxyl group (in XI) as corresponding to those substituents on the steroid. As it is considered unlikely that these two substituents have migrated from other positions to these during the dehydrogenation with palladium,[17] this result is evidence for the 1- and 4-positions of the hydroxyl and methyl group, respectively, of the 17-keto member of Inhoffen's phenolic steroids (V). This justifies the assignment of structures IV to XI to the compounds discussed in this paper and strengthens the conclusion[8] reached by Inhoffen that structure IV applies to all *x*-methyl-heterophenols prepared by Inhoffen's procedure from steroidal 1,4-diene-3-ones (I).

The configurations at carbons-8, -13 and -14 in IV might be expected to be the same as in cholesterol and consequently as in the estrogens. Carbon-9, however, was directly involved in the rearrangement and consequently an epimerization may or may not have taken place there, depending on the detailed mechanism of the dienone–phenol rearrangement in acetic anhydride. If this reaction belongs to the Wagner–Meerwein class, it is likely that the configuration at carbon-9 was retained[18] and that V is 1-hydroxy-4-methyl-3-desoxyestrone. If, on the other hand, the dienone–phenol rearrangement in acetic anhydride is more closely related to the Friedel–Crafts reaction[6] it is possible, though by no means certain, that an epimerization had taken place at carbon-9. Thus the possibility remains that V is 1-hydroxy-4-methyl-3-desoxy-9-isoestrone.

It is of interest that in this palladium dehydrogenation of VII at 300° the methoxyl group at carbon-1 was lost in a considerable portion of the product, while in several similar instances[12] a methoxyl group situated at carbon-3 remained intact even at 350°.[19]

Of the two demethoxylated products, one had the D ring still intact (IX) and the other had suffered a cleavage (X). Thus, VIII, IX and XI do not represent the logical consecutive intermediates of a single reaction course leading to X. This means that the demethoxylation and ring cleavage reaction compete with each other at 300°. Whether X arises from IX, from XI, or from both is not known at present. An attempt at effecting a demethoxylation of 4-methoxyphenanthrene by heating it with 5% palladium-on-charcoal at 350° resulted only in the recovery of some starting material.

When the palladium degradation of VII was carried out at 250–270°, VIII was the only product, though not isolated in high yield. At 350° the reaction resulted mostly in X and to a small extent in XI.

Experimental[20]

Rearrangement of 1,4-Androstadiene-3,17-dione (I, R = O) with Zinc Chloride in Acetic Anhydride and Acetic Acid.—A solution of 100 mg. of 1,4-androstadiene-3,17-dione

(14) W. Cocker, B. E. Cross, A. K. Fateen, C. Lipman, E. R. Stuart, W. H. Thompson and D. R. A. Whyte, *J. Chem. Soc.*, 1781 (1950).

(15) E. Heilbronner, U. Frolicher and Pl. A. Plattner, *Helv. Chim. Acta*, **32**, 2479 (1949).

(16) Before this methoxyphenanthrene had been definitely identified as XI, it was found not to be identical with a synthetic sample of 1-ethyl-2,5-dimethyl-8-methoxyphenanthrene (see J. Herran, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 899 (1951)). This was early evidence that Inhoffen's phenolic steroids did not have structure III.

(17) While the dehydrogenation of 4-methyl-1,2,3,4-tetrahydrophenanthrene with *selenium* has been reported to result in a shift of the methyl group from the 4 to the 1-position to give 1-methyl phenanthrene, the dehydrogenation of the same compound with *palladium* did not result in such a shift, the product being 4-methylphenanthrene. (For this and other examples, see Pl. A. Plattner, "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, pp. 39–40.)

(18) G. W. Wheland, "Advanced Organic Chemistry," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., p. 520.

(19) The loss of a methoxyl group attached to an aromatic ring during a relatively mild palladium-on-charcoal dehydrogenation is not frequently encountered. W. Cocker and co-workers have observed two other cases in the dehydrogenation of 1-ethyl-7,8-dimethyl-5-methoxy-1,2,3,4-tetrahydronaphthalene (see ref. 14) and of 1-ethyl-5,7-dimethyl-8-methoxy-1,2,3,4-tetrahydronaphthalene (W. Cocker, private communication).

(20) The melting points are not corrected. The analyses are by Micro-Tech Laboratories, Skokie, Ill.

(m.p. 136–137°[21]) in 5 cc. of acetic anhydride and 0.2 cc. of a 5% solution of anhydrous fused zinc chloride in glacial acetic acid was allowed to stand at room temperature under an atmosphere of nitrogen for 24 hours. The solution, which had turned brown, was diluted with 50 cc. of ether and extracted with ice-cold 10% sodium hydroxide solution until all the acetic anhydride had been decomposed and the acids extracted. After removal of the solvent, the residual crude acetate VI was heated in 10 cc. of 5% methanolic potassium hydroxide for one hour. Acidification and saturation with salt gave 92 mg. (92%) of crude 1-hydroxy-4-methyl-3-desoxyesterone (V), m.p. 230–235°. One recrystallization raised the melting point to 247–249° alone and when mixed with a sample prepared by the method of Djerassi and Scholz.[11,22]

In another experiment, conducted as described above on 500 mg. of I (R = O), the crude acetate (VI) was crystallized from petroleum ether (b.p. 30–60°) to give 400 mg. of almost colorless needles, m.p. 98–100°. Recrystallization from the same solvent gave a pure sample of **1-acetoxy-4-methyl-3-desoxyestrone (VI)**, m.p. 99–100°.

Anal. Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.00; H, 8.00.

The ultraviolet absorption spectrum of VI had a maximum at 268 mμ (ε 320) and a minimum at 252 mμ (ε = 200). Saponification as described above gave a quantitative yield of V.

Dehydrogenation of 1-Methoxy-4-methyl-3-desoxyestrone (VII) with 5% Palladium-on-Charcoal. (a) At 300°.—A mixture of 1.16 g. of VII (from the methylation[21] of V, obtained as described above) and 1.5 g. of 5% palladium-on-charcoal catalyst (all makes of this catalyst, which have been tried so far, have been successful in this degradation) was heated in the bottom of a six-inch test-tube under an atmosphere of nitrogen at 300 ± 5° for 20 minutes. The mixture was extracted with 50 cc. of benzene, and the extract, which had a slowly fading purple color and fluoresced violet in ultraviolet light, was filtered and concentrated to give an almost colorless glassy residue; yield 832 mg. A solution of the latter in 25 cc. of 5:1 petroleum ether (b.p. 30–60°)–benzene was passed through a column of 30 g. of activated alumina. Elution with the indicated solvents gave the following fractions:

1. 50 cc. p.e.–benz. (5:1) gave trace of oil
2. 25 cc. p.e.–benz. (1:1) gave 25 mg. colorless crystals
3. 50 cc. p.e.–benz. (1:5) gave 176 mg. colorless cryst. and oil
4. 25 cc. benzene gave 50 mg. oil
5. 30 cc. benz.–ether (1:1) gave 250 mg. oil
6. 100 cc. ether gave 50 mg. oil

Crystallization of fraction 2 from methanol yielded 20 mg. of **1-ethyl-2,8-dimethylphenanthrene (X)** as colorless plates, m.p. 117–118°, λ_{max}^{alc} 255, 262, 283, 294, 306 mμ (ε 69,000, 85,000, 17,000, 17,000, 22,000), λ_{infl}^{alc} 320–350 mμ (ε 250), λ_{min}^{alc} 234, 257, 278, 289, 299 mμ (ε 7,600, 50,000, 14,500, 11,250, 8,920).

Anal. Calcd. for $C_{18}H_{18}$: C, 92.25; H, 7.75. Found: C, 92.31; H, 7.78.

The mother liquor gave 13 mg. of the ***sym*-trinitrobenzene derivative of 1-ethyl-2,8-dimethylphenanthrene** as bright yellow needles, m.p. 168–169°.

Anal. Calcd. for $C_{24}H_{21}N_3O_6$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.41; H, 4.81; N, 9.29.

When fraction 3 was dissolved in methanol another crop of 1-ethyl-2,8-dimethylphenanthrene was obtained; yield 70 mg., m.p. 107–117°. Concentration of the mother liquor from this crystallization left an oil which formed the highly insoluble ***sym*-trinitrobenzene complex of 1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (XI)**, yield 140 mg., m.p. 189–193°. After recrystallization from a methanol–benzene mixture as bright yellow needles, the melting point was 196–197°.

Anal. Calcd. for $C_{25}H_{23}N_3O_7$: C, 62.88; H, 4.86; N, 8.80. Found: C, 62.67; H, 4.91; N, 8.70.

Fraction 4 was converted to the *sym*-trinitrobenzene derivative in a large volume of methanol, when 20 mg. of the insoluble derivative of XI precipitated, m.p. 185–195°. The mother liquor was combined with fractions 5 and 6 and treated as will be described further below. The methoxyphenanthrene XI was regenerated by reducing 110 mg. of its *sym*-trinitrobenzene complex in 6 cc. of ethanol with 1 g. of stannous chloride dihydrate in 7 cc. of concentrated hydrochloric acid at 60° until all the color had disappeared. Isolation by means of benzene and ether and purification by several washings with concentrated hydrochloric acid gave 45 mg. of colorless needles, m.p. 60–62°. Recrystallization from absolute ethanol yielded long, brittle and colorless needles of **1-ethyl-2,8-dimethyl-5-methoxyphenanthrene (XI)**, m.p. 64.5–65.5°, λ_{max}^{alc} 255, 281, 301, 314, 330, 346, 362 mμ (ε 66,200, 36,400, 15,200, 16,600, 1,660, 2,400, 2,580), λ_{min}^{alc} 232, 270, 297, 309, 326, 336, 353 mμ (ε 22,000, 23,500, 13,800, 11,200, 1,520, 956, 872).

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.60; H, 8.06.

The picrate of XI crystallized from ethanol as orange-red needles, m.p. 180.5–181.5°.

Anal. Calcd. for $C_{25}H_{23}N_3O_8$: C, 60.85; H, 4.70; N, 8.52. Found: C, 60.89; H, 4.80; N, 8.87.

Fractions 5 and 6, which had been combined with the mother liquor of the trinitrobenzene-complex-formation of fraction 4, were heated with additional *sym*-trinitrobenzene in alcohol to give 550 mg. of an orange-red complex, m.p. 120–135°. Recrystallization of a portion from methanol and then from petroleum ether containing a little ether afforded the ***sym*-trinitrobenzene complex of 1-methoxy-4-methyl-3-desoxyisoequilenin (VIII)**, m.p. 140–141°, as soft orange-red needles.

Anal. Calcd. for $C_{26}H_{25}N_3O_8$: C, 61.53; H, 4.97. Found: C, 61.89; H, 4.96.

Chemical reduction of this derivative in the crude form (m.p. 120–135°) by the above described procedure liberated **1-methoxy-4-methyl-3-desoxyisoequilenin (VIII)**, which crystallized from ethanol as colorless needles, m.p. 108–109°, λ_{max}^{alc} 223, 302, 320, 334 mμ (ε 50,880, 6,990, 5,080, 4,470), λ_{infl}^{alc} 238 mμ (ε 38,470), λ_{min}^{alc} 260, 315, 328 mμ (ε 1,600, 4,700, 3,400).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.74; H, 7.80.

From the ethanolic mother liquors of this crystallization it was possible to isolate 25 mg. of a higher-melting substance, which is presumably **4-methyl-3-desoxyisoequilenin (IX)**. It crystallized from ethanol as colorless needles, m.p. 143–145°, λ_{max}^{alc} 249, 255, 277, 287, 294, 309, 325 mμ (ε 3,800, 3,480, 6,610, 7,400, 5,900, 1,520, 1,260), λ_{infl}^{alc} 315 mμ (ε 1,000), λ_{min}^{alc} 244, 252, 257, 280, 292, 306, 320 mμ (ε 3,020, 3,000, 3,230, 6,300, 5,760, 1,380, 740).

Anal. Calcd. for $C_{19}H_{20}O$: C, 86.32; H, 7.63. Found: C, 86.37; H, 7.98.

(b) At 250–270°.—A mixture of 53 mg. of VII and 53 mg. of 5% palladium-on-charcoal was heated at 250° for eight minutes and at 270° for three minutes. Extraction with benzene yielded 48 mg. of an oil, from which 35 mg. (39%) of the *sym*-trinitrobenzene complex of 1-methoxy-4-methyl-3-desoxyisoequilenin (VIII) was obtained as orange-red needles, m.p. 138–140°. No attempt was made to account for the remaining material.

(c) At 350°.—Degradation of 300 mg. of VII with 300 mg. of 5% palladium-on-charcoal at 350° for ten minutes resulted in a partly crystalline residue, which was evaporatively distilled at 90–120° (0.3 mm.) and further purified by passage of a benzene solution through a column of 2 g. of activated alumina. The first few fractions afforded 80 mg. (33%) of 1-ethyl-2,8-dimethylphenanthrene (X) as colorless plates, m.p. 118–120°. When this experiment was repeated in the same manner with 100 mg. of VII and the crude product converted to the *sym*-trinitrobenzene complex in a large volume of hot methanol, 23 mg. (14%) of the characteristically insoluble yellow derivative of XI was obtained, m.p. 188–192°.

Attempted Demethoxylation of 4-Methoxyphenanthrene.—Treatment of 35 mg. of 4-methoxyphenanthrene (m.p. 66.5–67°)[23] with 50 mg. of 5% palladium-on-charcoal at 350° for six minutes resulted only in recovery of 20 mg. of the starting material, m.p. 65–67°.

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(21) We wish to thank the Schering Corporation, Bloomfield, N. J., for a gift of the 1,4-androstadiene-3,17-dione used in this investigation.

(22) We are grateful to Dr. Carl Djerassi for a generous sample of V.

(23) This sample was kindly placed at our disposal by Dr. Erich Mosettig.