stand overnight at room temperature, and acidified with hydrochloric acid in the manner previously described. The crude, gummy product was washed by decantation with water, suspended in about 30 ml. of 95% ethanol, and chilled at about −20° for one hour. The resulting 10 g. of solid product (24%, m.p. about 140°) was recrystallized from ethanol. The pure compound formed dense, virtually white crystals, m.p. 151–152°.

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.80, 67.68; H, 6.37, 6.38.

The **diethylaminoethyl ester hydrochloride (XVIII)** (procedure A) melted at 137–139°.

Anal. Calcd. for $C_{20}H_{30}O_4NCl$: C, 62.57; H, 7.88; N, 3.65. Found: C, 62.51, 62.49; H, 7.75, 7.74; N, 3.91, 3.92.

The **piperidinoethyl ester hydrochloride (XIX)** (procedure B) melted at 187–188°.

Anal. Calcd. for $C_{21}H_{30}O_4NCl$: C, 63.70; H, 7.64; N, 3.54. Found: C, 63.46; H, 7.49; N, 3.51, 3.47.

9-(*p*-Hydroxyphenyl)-7-keto-8-nonenoic Acid (X).—A solution of 51 g. of 7-ketocaprylic acid (VI), 35 g. of *p*-hydroxybenzaldehyde, 40 g. of sodium hydroxide and 650 ml. of water was heated on a steam-bath for four hours, allowed to stand overnight at room temperature, and acidified with hydrochloric acid in the manner previously described. The crude product consisted of 32 g. (42%) of a gummy solid, principal melting range 110–130°, plus a few grams of oil which was discarded. Successive crystallizations from dilute ethanol gave a good recovery of dense, white crystals of the pure compound, m.p. 133–135°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.76, 68.26, 68.50; H, 6.95, 6.67, 6.73.

The **diethylaminoethyl ester hydrochloride (XX)** (procedure B) melted at 124–125° and showed somewhat reduced solubility in water at room temperature.

Anal. Calcd. for $C_{21}H_{32}O_4NCl$: C, 63.38; H, 8.11. Found: C, 63.81, 63.56; H, 8.20, 8.20.

The **piperidinoethyl ester hydrochloride (XXI)** (procedure B) melted at 142–144° and showed somewhat reduced solubility in water at room temperature.

Anal. Calcd. for $C_{22}H_{32}O_4NCl$: C, 64.45; H, 7.87; N, 3.42. Found: C, 64.25, 64.06; H, 7.79, 7.71; N, 3.30, 3.30.

Ozonolysis of 6-(*p*-Hydroxyphenyl)-4-keto-5-hexenoic Acid (VII).—A solution of 110 mg. of VII in 30 ml. of ethyl acetate, maintained at −10 to −15°, was treated with 98% of the calculated amount of ozone. After removal of the solvent, the waxy ozonide was decomposed by heating it with water on the steam-bath for 30 minutes. The resulting solution was cooled, treated with potassium carbonate solution and hydrogen peroxide, allowed to stand at room temperature for 30 minutes, acidified with hydrochloric acid, and evaporated to dryness. The organic portion of the residue was removed by digestion with acetone, and the material thus obtained was subjected to chromatography on a column prepared with five grams of silica. Elution with 10:1 benzene–acetone resulted in the isolation of 21 mg. (38%) of slightly impure hydroquinone, identified by its characteristic conversion to quinhydrone.

Elution with 6:1 benzene–acetone resulted in the isolation of 28 mg. (47%) of almost pure succinic acid. After one recrystallization it melted at 187–188° and did not depress the melting point of an authentic sample. For further confirmation of its identity it was converted to the diphenacyl ester, m.p. 147–149°.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE ROLLIN H. STEVENS MEMORIAL LABORATORY OF THE DETROIT INSTITUTE OF CANCER RESEARCH AND FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

The Dienone–Phenol Rearrangement with Mineral Acids[1,2]

BY ANDRE S. DREIDING, WALTER J. PUMMER AND ARTHUR J. TOMASEWSKI

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The aromatization of 1,4-androstadiene-3,17-dione with aqueous mineral acids yielded mostly 1-methylestrone and also some 1-hydroxy-4-methyl-3-desoxyestrone. Under the same conditions, 10-methyl-2-keto-$\Delta^{1:9,3:4}$-hexahydronaphthalene rearranged to 4-methyl-ar-2-tetralol and a small amount of 4-methyl-ar-1-tetralol. The differences between aqueous acid and anhydrous media for the dienone–phenol rearrangement are discussed.

The media which have been used for the acid-catalyzed aromatization of cyclohexadienones can be divided into two types: (a) aqueous mineral acids, and (b) anhydrous media such as acetic anhydride with an acid catalyst. In the one case where both media were applied to the same compound, santonin,[3,4] the result was the same and the dienone–phenol rearrangement was formulated as a general acid-catalyzed reaction.[5,6] The present experiments show that the course of this reaction may depend on the nature of the medium.

Only anhydrous acid conditions have been extensively applied to steroids. While it was originally thought that this method transformed steroidal 1,4-diene-3-ones (such as I) into 1-methyl-3-hydroxysteroids (such as III),[7,8] it is now known that the products actually are 1-hydroxy-4-methylsteroids (such as II).[6,9] The 1-methyl-3-hydroxysteroids could be prepared by this method only when an additional double bond was present at the 6,7-position.[10]

The direct conversion of I into III can be accomplished in 55% yield by the use of concentrated aqueous hydrochloric or hydrobromic acid, in which I is readily soluble. A small amount (10%) of II is also formed. The two phenolic steroids were separated by taking advantage of the greater alkali solubility of III or by chromatographic ad-

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[2] This work was supported in part by a Research and Development Contract between the Detroit Institute of Cancer Research and the United States Atomic Energy Commission. Support was also provided by institutional grants from the Michigan Cancer Foundation, The American Cancer Society, Inc., and the S. S. Kresge Foundation.

[3] A. Andreocci, *Gazz. chim. ital.*, **23**, II, 469 (1893); **25**, I, 452 (1895); A. Andreocci and P. Bertolo, *Ber.*, **31**, 3131 (1898); G. Bargellini and A. Mannino, *Gazz. chim. ital.*, **39**, II, 101 (1901).

[4] Huang-Minlon, Chien-Pen Lo and L. Ju-Yung Chu, THIS JOURNAL, **65**, 178 (1943).

[5] R. T. Arnold, J. S. Buckley and J. R. Richter, *ibid.*, **69**, 2322 (1947); Huang-Minlon, *ibid.*, **70**, 611 (1948).

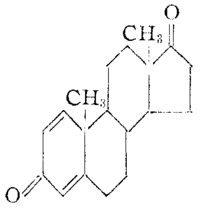
[6] R. B. Woodward and T. Singh, *ibid.*, **72**, 494 (1950).

[7] H. H. Inhoffen and Huang-Minlon, *Naturwissenschaften*, **26**, 756 (1938); *Ber.*, **74**, 604 (1941).

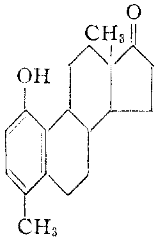
[8] C. Djerassi and C. R. Scholz, *J. Org. Chem.*, **13**, 704 (1948).

[9] A. S. Dreiding, A. Voltman and A. J. Tomasewski, THIS JOURNAL, **75**, not published (1953); H. H. Inhoffen, *Angew. Chem.*, **63**, 297 (1951); J. Herran, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Org. Chem.*, **16**, 899 (1951).

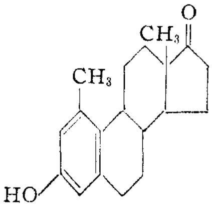
[10] C. Djerassi, G. Rosenkranz, J. Romo, J. Pataki and St. Kaufmann, THIS JOURNAL, **72**, 4540 (1950).



I



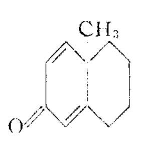
II



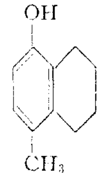
III

sorption of their methyl ethers. They can be distinguished by their infrared absorption spectra. A fairly strong band in the 11.67–11.76 μ region, which may be due to isolated hydrogens on a benzene ring,[11] is present in III but not in II, while a strong peak near 12.28–12.45 μ, due to two adjacent hydrogens on a benzene ring,[11] shows in II but not in III. The methyl ethers of II and III and the two tetralols V and VI exhibit the same differences in light absorption.

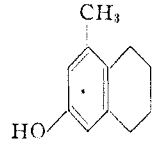
In order to test the generality of the effect of the reaction medium on the course of the dienone–phenol rearrangement the aqueous mineral acid procedure was applied to 10-methyl-2-keto-$\Delta^{1:9,3:4}$-hexahydronaphthalene (IV). Woodward and Singh have shown that the acetic anhydride–sulfuric acid method rearranged this ketone to



IV



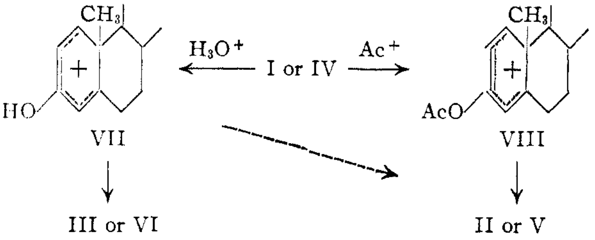
V



VI

4-methyl-ar-1-tetralol (V) as the acetate.[6] In contrast, 4-methyl-ar-2-tetralol (VI) was the major product (62%) when the aromatization was conducted in concentrated hydrochloric acid or 50% sulfuric acid. In both reactions a small amount of V could be shown to be present.[12]

The manner in which the reaction medium influences the course of the dienone–phenol rearrangement is not yet clear. In an aqueous acid solution the dienones are probably attacked by a hydronium ion to give an intermediate formulated as VII, while in acetic anhydride the intermediate is more likely VIII. From this point on, the two aromatizations differ in three respects: (1) The number of hydrogens on the migrating carbon atom, (2) the location of the migrating group with respect to the plane of the dienone ring, and (3) the nature of the shift itself. Thus the intermediate VII suffers a preferential migration of a methyl group on one side of the dienone ring by a 1,2-shift to give III or VI, while VIII is converted exclusively into II or V by a 1,3-shift of a secondary (or primary) carbon atom on the other face of the unsaturated ring. More evidence is needed to establish whether electrical or steric differences inherent in the two situations (expressed tentatively as VII and VIII) are responsible for the separate reaction paths.[16]



Experimental[17]

Rearrangement of 1,4-Androstadiene-3,17-dione (I). (a). With Hydrobromic Acid.—A clear red solution of 421 mg. of I (m.p. 134–139°)[18] in 6 cc. of 48% hydrobromic acid was allowed to stand at room temperature in a stoppered flask for five days. A first crop of 143 mg. of almost black solid was collected. It turned to a tan gray on washing with water. The mother liquor was heated at 55° for 24 hours when a second crop of 246 mg. was collected. Further heating for two days at 55° yielded 12 mg. which brought the total yield to 95%. This solid material, m.p. 180–220° (shrinking at 140°), apparently consisted mostly of phenols; $\lambda_{\max}^{\text{alc}}$ 285 mμ, ε 2000; $\lambda_{\min}^{\text{alc}}$ 252 mμ, ε 500.

A portion of this crude product (385 mg.) was heated with 75 cc. of 5% sodium hydroxide at 100° for two hours and cooled. The dark insoluble material was filtered off and the clear amber filtrate was acidified yielding 250 mg. of a cream colored powder, m.p. 210–232°, which consisted mostly of 1-methylestrone (III). Recrystallization from methanol afforded 223 mg. (55%) of 1-methylestrone as pale yellow prisms, m.p. 246–249°, alone and when mixed with an authentic sample of III, m.p. 248–250°.[19] When the product was mixed with a sample of II (prepared from I by the acetic anhydride–zinc chloride rearrangement, m.p. 247–249°) it melted at 205–220°. The material in the methanolic mother liquors melted lower and probably was a mixture of III and II.

The alkali insoluble substance was washed through the filter with chloroform and the solvent was evaporated. When the residue was covered with a little methanol it yielded elongated tan prisms, m.p. 237–243°; yield 46 mg. (11%). This consisted mostly of 1-hydroxy-4-methyl-3-desoxyestrone (II); after recrystallization from methanol, it melted at 245–249° alone and when mixed with an authentic sample of II. The methanolic mother liquors yielded 50 mg. of a yellow powder which was very soluble in methanol and was not further investigated.

In order to test the efficiency of separating II and III in the previous experiment 58 mg. of II was heated with 10 cc. of 5% sodium hydroxide for two hours at 100° and cooled. The insoluble material, after washing with 2 cc. of 5% so-

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[11] N. B. Colthup, *J. Optical Soc.*, **40**, 397 (1950).

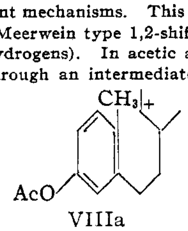
[12] There have been two reports of a conversion of IV into VI by the use of concentrated hydrochloric acid. One of them[13] has been seriously questioned[6,14] and the other one,[15] an abstract of which appeared as this paper was being written, described a 10% yield.

[13] K. Paranjpe, N. L. Phalnikar, B. V. Bhide and K. S. Nargund, *Rasayanam*, **1**, 233 (1943).

[14] A. L. Wilds and C. Djerassi, THIS JOURNAL, **68**, 1715 (1946).

[15] Y. Abe, T. Harukawa and T. Toga, *J. Pharm. Soc. Japan*, **71**, 471 (1951); *C. A.*, **46**, 4518 (1952).

[16] The possibility might be considered that the two aromatizations proceed by different mechanisms. This hypothesis suggests that VII favors a Wagner–Meerwein type 1,2-shift (simplest path) of the methyl group (most hydrogens). In acetic anhydride, however, the reaction might pass through an intermediate VIIIa (similar to one postulated by Woodward[6]), which would probably favor the migration of the secondary (or primary) carbon atom by the only path available to it, a 1,3-shift.



VIIIa

[17] The melting points are reported without correction as observed in capillary tubes. The microanalyses are by Micro-Tech Laboratories, Skokie, Illinois.

[18] We are grateful to the Schering Corporation, Bloomfield, N. J., for a generous gift of 1,4-androstadiene-3,17-dione.

[19] An authentic sample of 1-methylestrone[10] was kindly supplied by Dr. Carl Djerassi and Syntex, S.A., Mexico, D.F.

dium hydroxide and 2 cc. of water and drying, weighed 53 mg. (91%). Acidification of the clear mother liquor gave 4 mg. (7%) of II, which would not dissolve on heating with 0.8 cc. of 5% sodium hydroxide.

Under the same conditions 62 mg. of III dissolved completely in 5 cc. of 5% sodium hydroxide and was recovered quantitatively on acidification.

(b) **With Hydrochloric Acid.**—When the rearrangement was conducted in concentrated hydrochloric acid (25 cc. for 500 mg. of I) at room temperature for 25 days, the yield of precipitated phenolic material was 394 mg. (79%), m.p. 125–215°, $\lambda_{\max}^{\text{alc}}$ 285 mμ, ϵ 2000, $\lambda_{\min}^{\text{alc}}$ 252 mμ, ϵ 500. The alkaline extraction procedure as described in the previous experiment afforded 241 (48%) of crude 1-methylestrone (III), m.p. 205–225°. Its infrared absorption spectrum was identical with an authentic sample,[10] and its acetate melted at 155–157° alone and when mixed with an authentic sample, m.p. 157.5–158.5°.[10] The yield of alkali insoluble material was 128 mg., m.p. 185–201°. That this consisted largely of 1-hydroxy-4-methyl-3-desoxyestrone (II) was shown by the similarity of its infrared absorption spectrum with that of a pure sample of II and by the fact that its benzoate, m.p. 234.5–236°, did not depress the melting point of the **benzoate of II**, which crystallized from benzene–petroleum ether as colorless needles, m.p. 234.5–236°.

Anal. Calcd. for $C_{26}H_{28}O_3$: C, 80.38; H, 7.27. Found: C, 80.36; H, 7.40.

In another experiment a solution of 300 mg. of I was heated in 10 cc. of constant boiling hydrochloric acid under reflux for two hours. The precipitated product (233 mg.) was converted to the methyl ethers of II and III, m.p. 80–95°, yield 173 mg. (55%). Chromatographic separation on activated alumina with a 1:1 mixture of petroleum ether and benzene gave 40 mg. of the methyl ether of II, which after recrystallization from petroleum ether melted at 115–117° alone and when mixed with an authentic sample (reported,[8] m.p. 117–118°). Further elution of the column with benzene yielded 90 mg. of the **methyl ether of III**, m.p. 126–127°, which did not depress the melting point of the methyl ether prepared from an authentic sample of III with dimethyl sulfate and sodium hydroxide, m.p. 126–127.5°.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.78. Found: C, 80.77; H, 8.88.

(c) **With Hydrochloric and Acetic Acid.**—When a solution of 100 mg. of I in 1.5 cc. of glacial acetic acid, 0.2 cc. of water and 0.5 cc. of concentrated hydrochloric acid was refluxed for six hours it remained clear. Dilution with water precipitated 93 mg. of a tan solid, m.p. 194–200°. In this case, the two phenols were separated by fractional crystallization from aqueous alcohol, which eventually yielded 35 mg. of III, m.p. 242.5–245°, and 10 mg. of II, m.p. 240–244°. These samples did not depress the melting points of the corresponding authentic steroids.

Rearrangement of 10-Methyl-2-keto-$\Delta^{1:9,3:4}$-hexahydronaphthalene (IV). (a) **With Hydrochloric Acid.**—A clear yellow solution of 500 mg. of IV[6] (m.p. 14–15°) in 5 cc. of concentrated hydrochloric acid was heated at 100° for 30 minutes, causing a dark oil to separate. After dilution with water, the product was isolated with ether and dissolved in 30 cc. of 3% aqueous sodium hydroxide. Acidification and ether extraction yielded an oil which solidified on triturating with petroleum ether to give 320 mg. (64%) of a colorless solid mixture of V and VI, m.p. 96–100°. Recrystallization from the same solvent afforded 233 mg. (47%) of 4-methyl-ar-2-tetralol (VI), m.p. 104–105° alone and when mixed with an authentic sample,[6] m.p. 104–105°, $\lambda_{\max}^{\text{alc}}$ 281 mμ, ϵ 2000, $\lambda_{\min}^{\text{alc}}$ 251 mμ, ϵ 250. The *p*-nitrobenzoate melted at 114–116° alone and when mixed with an authentic sample,[20] m.p. 116–118°.

The material contained in the combined mother liquors was converted to the *p*-nitrobenzoate, yield 250 mg. (26%) of solid, m.p. 96–99°. Several recrystallizations in high yields raised the melting point not further than 104–106°. This substance, which crystallizes from ethanol as yellow needles, analyzed correctly for a *p*-nitrobenzoate of a methyltetralol, but depressed the melting point of this derivative of either V or VI.

Anal. Calcd. for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.60; H, 5.77; N, 4.72.

That this substance contained approximately equal quantities of the *p*-nitrobenzoates of V and VI, which had crystallized together, was shown as follows: (a) a 1:1 mixture of V and VI gave the same compound, m.p. and mixed m.p. 104–106°, when converted to the *p*-nitrobenzoate. (b) In a series of mixed melting points of the pure derivatives of V (m.p. 145–147°) and of VI (m.p. 115–117°) only the 1:1 mixture melted at 102–105°.

These results indicated that the rearrangement resulted in a total yield of 62% of 4-methyl-ar-2-tetralol (VI) and approximately 10% of 4-methyl-ar-1-tetralol (V).

(b) **With 50% Sulfuric Acid.**—When the rearrrangement was performed as described in the previous experiment, except that 50% sulfuric acid was used instead of the concentrated hydrochloric acid, there resulted 260 mg (52%) of 4-methyl-ar-2-tetralol (VI), m.p. 105–106°, and 335 mg. of the mixed *p*-nitrobenzoates of V and VI, described above, m.p. 104–106°.

Infrared Absorption Spectra.—The spectra were measured in a Beckman I.R. 2 instrument and interpreted by Mr. Bruce Scott of Parke, Davis and Co. The pure samples showed the following characteristic absorption bands: 1-methylestrone (III), $\lambda_{\max}^{\text{mineral oil}}$ 11.67 μ; methyl ether of III, $\lambda_{\max}^{\text{mineral oil}}$ 11.74 μ; 4-methyl-ar-2-tetralol, $\lambda_{\max}^{\text{mineral oil}}$ 11.76 μ; 1-hydroxy-4-methyl-3-desoxyestrone (II), $\lambda_{\max}^{\text{mineral oil}}$ 12.28 μ; methyl ether of II, $\lambda_{\max}^{\text{mineral oil}}$ 12.45 μ; 4-methyl-ar-1-tetralol, $\lambda_{\max}^{\text{mineral oil}}$ 12.40 μ.

DETROIT, MICHIGAN

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[20] A. Sandoval, L. Miramontes, G. Rosenkranz and C. Djerassi. THIS JOURNAL, **73**, 990 (1951).