meric residue. The distillate crystallized almost completely on standing and after three recrystallizations melted at 103–104°.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00; CH_3O, 25.20. Found: C, 77.87; H, 8.92; CH_3O, 25.09.

One stereoisomer of 5,8-dimethoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XI) has been previously prepared and reported to melt at 106–107°.[16]

The infrared curves[17] for each cyclization product were compared and found to differ in the region 7–11μ. All of the principal bands of the mixture from cyclization of alcohol VII could be assigned to either spirane X or phenanthrene XI.[18]

Dehydrogenations.—A mixture of the cyclization product (500 mg.), diphenylamine (2 g.) and palladium on charcoal (100 mg., 5%) was heated at 300–315° for six hours while a current of carbon dioxide was passed through the dehydrogenator.[19] The product was washed out with ether, the catalyst filtered and dry hydrogen chloride passed in to precipitate diphenylamine hydrochloride. The ether was evaporated and the crude dehydrogenation product placed on a column of acid-washed alumina (*ca.* 30 g.) with ligroin. Elution with 5% benzene in petroleum ether (80 ml.) removed any starting material and pure benzene (80 ml.) washed out the dehydrogenation product.

Cyclization product X (m.p. 112–113°, from alcohol III) was recovered unchanged in 85% yield.

Cyclization product IX (m.p. 58–59° from alcohols IV and VIII) produced 1,4-dimethoxyphenanthrene (XII) which melted at 123.5–124.5°.[16] Selenium at 360° also formed XII in good yield. The characteristic brown picrate melted at 164–166° in agreement with the reported value.[16]

Cyclization product XI (230 mg.) yielded 157 mg. of 1,4-dimethoxyphenanthrene (m.p. 124–125°) when the dehydrogenation was continued for three hours at 295–305°.

The mixture of product from the cyclization of VII was dehydrogenated to yield spirane X (*ca.* 300 mg.) and 1,4-dimethoxyphenanthrene (*ca.* 100 mg.).

β-(*p*-Methoxyphenyl)-ethyl Bromide.[20]—The procedure was the same as for bromide II. From β-(*p*-methoxyphenyl)-ethanol[21] (75 g., m.p. 24°) there was obtained 67 g. (63%) of bromide which boiled at 133–136° (11 mm.).[21]

1-β-(*p*-Methoxyphenyl)-ethyl-1-cyclohexanol.[20]—Freshly distilled cyclohexanone (6.9 g.) was added to the cold Grignard reagent prepared from magnesium (1.7 g.), dry ether (150 ml.) and β-(*p*-methoxyphenyl)-ethyl bromide (15 g.). When the addition was complete the reaction mixture was refluxed for one hour and then decomposed with ammonium chloride solution. Fractionation of the dried organic layer yielded 6.5 g. (42%) of product which boiled at 164–168° (1 mm.), m.p. 59–60°.

Anal. Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.16; H, 9.62.

From the distillation residue there was isolated a crystalline substance believed to be 1,4-di-(*p*-methoxyphenyl)-butane which melted at 78–79° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.52; H, 8.20.

6-Methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene.[20]—1-β-(*p*-Methoxyphenyl)-ethyl-1-cyclohexanol (5 g.) was treated with 83% sulfuric acid (25 ml.) at −5° for 20 minutes with stirring. The mixture was extracted with petroleum ether to yield 2.5 g. (50%) of cyclization product which boiled at 135–138° (1.5 mm.).

Anal. Calcd. for $C_{15}H_{12}O$: C, 83.28; H, 9.32. Found: C, 82.92; H, 9.05.

A sample of this product was dehydrogenated by using palladium on charcoal at 330° for three hours.[22] During the reaction some material sublimed onto the condenser. This proved to be mainly phenanthrene which melted at 98–100° after recrystallization from methanol and was identical with an authentic sample. From the liquid dehydrogenation product 3-methoxyphenanthrene (m.p. 58–59°) was isolated by forming the picrate (m.p. 125–127°)[23] which was decomposed with ether and dilute ammonia.

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[16] C. A. Grob, W. Jundt and H. Wicki, *Helv. Chim. Acta*, **32**, 2427 (1949).

[17] The infrared spectral measurements were made by Mr. Felix Borek using a Perkin-Elmer double beam model 21 recording spectrophotometer.

[18] Bands in microns for which the transmittance was less than 60% (5% solutions in chloroform): (X)—7.53, 7.60, 8.01, 9.08, 9.30, 9.64, 9.73, 10.37; (XI)—7.98, 8.82, 8.92, 9.23, 9.39; (mixture from alcohol VII)—7.55, 7.98, 8.82, 8.92, 9.08, 9.26, 9.37, 9.63, 9.73, 10.37.

[19] L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., New York, N. Y., 1941, pp. 462.

[20] Experiment carried out by L. Gordon.

[21] K. H. Slotta and H. Heller, *Ber.*, **63**, 3029 (1930).

[22] The aromatization of spiranes to phenanthrenes usually does not occur under these conditions; therefore this experiment is believed to indicate that the octahydrophenanthrene is the major cyclization product.

[23] R. Pschorr and A. Klein, *Ber.*, **34**, 4006 (1901), report the melting point of 3-methoxyphenanthrene as 59° and the melting point of the picrate as 124–125°.

NEW BRUNSWICK, N. J.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MONTANA STATE UNIVERSITY]

Synthetic Estrogens. I. Derivatives of 1-Phenylphenanthrene

BY RICHARD E. JUDAY

RECEIVED JANUARY 2, 1953

A number of derivatives of 1-phenylphenanthrene have been prepared. A condensation between 6-methoxy-α-tetralone and anisalacetone was found to be a satisfactory reaction for preparing the hexa- and octahydro- derivatives of 1-phenylphenanthrene. Three of the four compounds tested showed activity in 1 mg. doses.

In view of the high estrogenic activity found by Stuart and co-workers for the four diastereomeric racemates of 2,4-di-(*p*-hydroxyphenyl)-3-ethylhexane[1] (I) it seemed of interest to determine whether hydroaromatic compounds analogous to I, such as II, would have similar activity.

The most convenient approach to II appeared to be the method developed by Rapson and Robinson[2] starting with 6-methoxy-α-tetralone and anisalacetone. The original conditions of the reaction produced only a trace of solid product. However, by adding dimethylamine to the reaction mixture, and by giving the anisalacetone a preliminary treatment with excess dimethylamine in order to form the unstable Mannich base, the yield of solid product was raised to 54%. This compound formed a red dinitrophenylhydrazone, and had an ultraviolet absorption spectrum similar to that of anisalacetone,[3] except for a secondary maximum at

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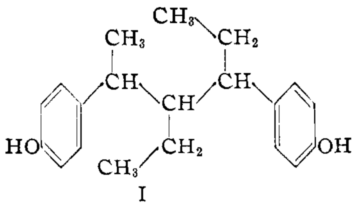
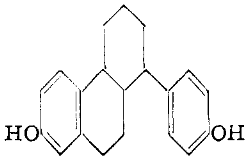
[1] A. H. Stuart, A. J. Shukis, R. C. Tallman, C. McCann and G. R. Treves, THIS JOURNAL, **68**, 729 (1946).

[2] W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1285 (1935).

[3] A. L. Wilds, L. W. Beck, W. J. Close, C. Djerassi, J. A. Johnson, T. L. Johnson and C. H. Shunk, THIS JOURNAL, **69**, 1985 (1947).

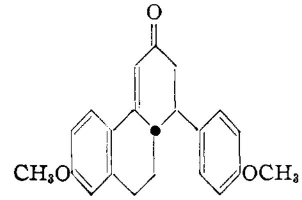


I

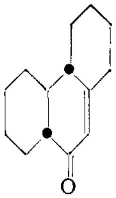


II

223 mμ, indicating that it was the expected 1-(*p*-methoxyphenyl)-3-keto-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene (III). A *trans* configuration between C_1–C_{10a} may be tentatively assigned to III on the basis of the work of Linstead and coworkers,[4] who showed that for the condensation of 1-acetyl-Δ^1-cyclohexene with cyclohexanone to form IV[2] the *trans, anti* isomer was formed.

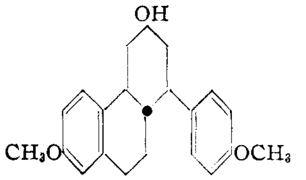


III

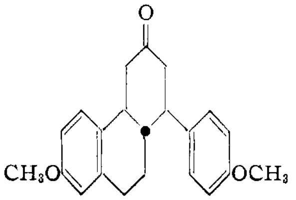


IV

Since attempts to reduce the C_4–C_{4a} double bond of III selectively were not satisfactory, it was found convenient to reduce III completely to form the alcohol V which was oxidized by the Oppenauer method to the ketone VI.

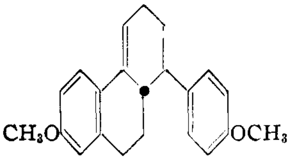


V

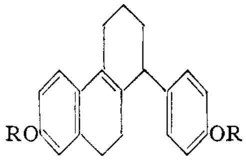


VI

The ketone could be reduced to the octahydrophenanthrene derivative VII, m.p. 134.5°, using the technique of Huang-Minlon.[5] Sodium–alcohol reduction of III gave only an oil. In order to reduce the ketone group of III a modification of the Huang-Minlon technique[5] was required since no solid product could be obtained using potassium hydroxide and only a yield of 15% with sodium hydroxide. Lithium hydroxide was found to be too weak to catalyze the reaction and the hydroxides of calcium and strontium too insoluble. Barium hydroxide was found to be satisfactory, giving yields of the hexahydrophenanthrene derivatives IX, m.p. 119° and X, m.p. 77.8°, totalling 45%, with IX being the principal product formed. Barium hydroxide cannot be considered as a general catalyst for the reduction of unsaturated ketones as it failed with succinoylcyclohexene. Rigid exclusion of water was necessary for optimum yields, so the barium hydroxide was given a preliminary dehydration by dissolving in diethylene glycol and distilling the solution in an inert atmosphere until a temperature of 245° was reached. It was also found desirable to use anhydrous hydrazine rather than the hydrate. The use of barium hydroxide has an additional advantage in that the ether groups are not cleaved so that remethylation is unnecessary. The reaction can also be run for shorter periods of time at higher temperature without lowering the yield. In general, the reactions were run at the boiling point of diethylene glycol (245°) for no more than 45 minutes.



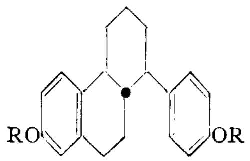
IX



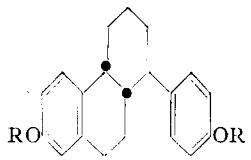
X, R = CH_3
XI, R = H

The location of the double bond in IX and X could best be determined from a consideration of the ultraviolet spectra. Woodward and Eastman,[6] Hogg[6b] and Heer and Miescher[6c] have shown that for similar compounds, when the double bond is in the *endo* position, there is an absorption maximum at 272–275 mμ. Heer and Miescher[6c] have also shown that there is an absorption maximum at 264 mμ when the double bond is in the *exo* position. In this case, IX showed a maximum at 263.5 mμ, and X at 275.5 mμ.

Attempts to rearrange and dehydrogenate IX to form the tetrahydrophenanthrene derivative XV at low temperatures using palladium–charcoal as catalyst with acetone[7] or cyclohexene as hydrogen acceptors were unsuccessful as the reaction proceeded by disproportionation, the principal product isolated being the octahydrophenanthrene derivative XII, m.p. 153.5°, an isomer of VII.



VII, R = CH_3
VIII, R = H



XII, R = CH_3
XIII, R = H

Hydrogenation of IX in neutral medium produced XII as the principal product, while VII and XII were formed in approximately equal quantities when acetic acid was added to the reaction medium.

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[4] (a) R. P. Linstead and A. L. Walpole, *J. Chem. Soc.*, 842 (1939); (b) R. P. Linstead and A. L. Walpole, *ibid.*, 850 (1939); (c) R. P. Linstead and W. E. Doering, THIS JOURNAL, **64**, 1991 (1942).

[5] Huang-Minlon, *ibid.*, **68**, 2487 (1946).

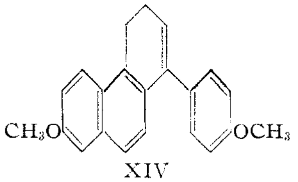
[6] (a) R. B. Woodward and R. H. Eastman, *ibid.*, **66**, 674 (1944); (b) J. A. Hogg, *ibid.*, **71**, 1918 (1949); (c) J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219 (1948).

[7] J. Heer and K. Miescher, *ibid.*, **31**, 1289 (1948).

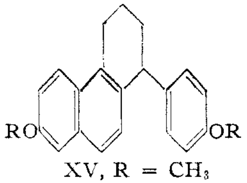
The B:C fusions of VII and XII can best be determined from the results obtained on hydrogenation of X and XI, which would be expected to give *cis* configurations only. Reduction of X in neutral medium produced XII in a yield of 90%. The configuration formed on the reduction of XI was also determined because the double bond seems to be more firmly located in the *endo* position than in X, thus excluding any possible rearrangement of the double bond to the *exo* position which might occur in X in advance of reduction. Again, XII was obtained after the reduction product was remethylated, this time in an over-all yield of 50%. In neither case could any VII be isolated. On this basis a *cis* configuration may be assigned to XII and the *trans* configuration to VII.

The *trans* B:C fusion assigned to VII could not be predicted from the results obtained by hydrogenating III, since the isomer formed depends more on the structure of the molecule as a whole rather than on the presence of the α-β unsaturated ketone grouping. Linstead and co-workers have shown[4b,c] by conversion to a perhydrodiphenic acid, that reduction of IV gives rise to a *trans* B:C fusion. Prelog and Zimmermann[8] and DuFeu, McQuillan and Robinson[9] have shown for other compounds containing this grouping that the *cis* configuration is formed. Wilds, Johnson and Sutton[10] have found that for ring D unsaturated equilenin either a *cis* or *trans* ring fusion may predominate depending on whether the reduction is carried out in basic or acidic medium. When III was hydrogenated only the *trans* isomer was isolated in both acid and alkaline medium.

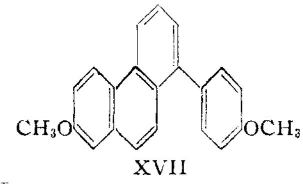
Because of the failure of VII to undergo dehydrogenation to form XV, 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene was used as starting material. Reaction with the Grignard reagent from *p*-bromoanisole produced a carbinol which was readily dehydrated with warm acetic anhydride to give the dihydrophenanthrene derivative XIV. Hydrogenation of XIV gave the tetrahydrophenanthrene derivative XV which was readily dehydrogenated by sulfur at 170–230° to form 1-(*p*-methoxyphenyl)-7-methoxyphenanthrene (XVII). The octahydrophenanthrene derivative XII could also be dehydrogenated by sulfur at 170–230° to form XVII.



XIV



XV, R = CH_3
XVI, R = H



XVII

The methoxyl groups of the octahydrophenanthrene compounds VII and XII were readily cleaved by refluxing in hydrobromic acid–acetic acid solution to give almost quantitative yields of the corresponding phenols VIII and XIII. It was necessary to use potassium hydroxide in diethylene glycol to cleave the methoxyl groups of IX because of its sensitivity to acid. Treatment for 13 minutes at 245° was sufficient to form the phenol XI. In the course of the reaction the double bond shifted to the *endo* position, which was proven by the shift in the absorption maximum to 275.5 mμ, and by remethylation with methyl *p*-toluenesulfonate to yield X rather than IX. The methoxyl groups of XV could best be cleaved by heating with pyridine hydrochloride at 195° to form the phenol XVI.

The results of the bioassays for the estrogenic activity are given in Table I.

TABLE I

ESTROGENIC ACTIVITIES OF 1-(*p*-HYDROXYPHENYL)-7-HYDROXYHYDROPHENANTHRENES

	Compound	Total dose,[a] mg.	No. of animals	Positive response
1	*cis,anti*(?)-1,2,3,4,4a,9,10,-10a-Octahydro-(XIII)	0.5	10	below 50 %
		1.0	21	52
2	*trans,anti*(?)-1,2,3,4,4a,9,10,10a-Octahydro-(VIII)	1.0	10	–
		2.0	12	33
3	1,2,3,4,9,10-Hexahydro-(XI)	1.0	20	35
		1.5	10	80
4	1,2,3,4-Tetrahydro-(XVI)	1.0	20	30
		2.0	10	50
5	Estrone controls	0.001	16	Over 50

[a] Two doses injected subcutaneously in sesame oil into rats; activity indicated by positive vaginal smears.

It will be noted that the compound to which the *trans* configuration of the B:C ring is assigned was inactive at the dosage level used while the other three compounds showed the same activity, about 1/1000 that of estrone. All compounds are much less active than the four diasteromeric racemates of 2,4-di-(*p*-hydroxyphenyl)-3-ethylhexane,[1] which possesses activities ranging from 0.8 to 35 micrograms minimum effective dose. This same diminution in activity when going from an aliphatic derivative to the ring-closed analog has been noted by Wilds and Sutton[11] who observed a decrease of the same order of magnitude between hexestrol and the ring-closed analogs *cis*- and *trans*-2,8-dihydroxyhexahydrochrysene.[12] Diethylstilbestrol is also about 100 times more active than 2,8-dihydroxy-5,6-11,12-tetrahydrochrysene. A possible explanation for this phenomenon is that where a molecule differs slightly in shape from the naturally occurring estrogen, the bonds of an aliphatic compound can be deformed enough to meet space requirements, while the analogous ring-closed molecule is too rigid.

Acknowledgments.—The author is indebted to the Research Corporation and the research committee of Montana State University for funds to

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(8) V. Prelog and M. Zimmermann, THIS JOURNAL, **32**, 2360 (1949).

(9) E. C. DuFeu, F. J. McQuillan and R. Robinson, *J. Chem. Soc.*, 53 (1937).

(10) A. L. Wilds, J. A. Johnson and R. E. Sutton, THIS JOURNAL, **72**, 5524 (1950).

(11) A. L. Wilds and R. E. Sutton, *J. Org. Chem.*, **16**, 1371 (1951).

(12) E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939).

support this work, and wishes to express his gratitude to Drs. L. Earle Arnow, and J. M. Sprague of Sharp and Dohme, Inc., for the estrogenic assays.

Experimental[13]

6-Methoxy-α-tetralone.—α-Naphthyl methyl ether was reduced using the method of Stork[14] and the resulting 6-methoxytetralin oxidized by the method of Burnop, Elliot and Linstead.[15] The oxidation product was recovered using the method of Schwenk and Papa.[16] The crude 6-methoxy-α-tetralone was then distilled *in vacuo* and recrystallized from methanol, m.p. 77–78.5°.

trans(?)**-1-(*p*-Methoxyphenyl)-3-keto-7-methoxy-1,2,3,-9,10,10a-hexahydrophenanthrene (III).**—To 34.3 g. (0.194 mole) of anisalacetone, m.p. 72.6–73.5°, in a pressure bottle was added 40 ml. (0.604 mole) of anhydrous dimethylamine. The resulting solution was allowed to stand overnight at room temperature.

To a solution of 39.0 g. (0.22 mole) of 6-methoxy-α-tetralone in 150 ml. of dry benzene was added 7.4 g. (0.192 mole) of sodamide and the mixture refluxed with stirring, in an argon atmosphere, for seven hours. The mixture was cooled, diluted with 70 ml. of dry ether and then cooled to −30° in a Dry Ice–acetone bath. Anhydrous dimethylamine (10 ml.) was then added. The solution of anisalacetone in dimethylamine was diluted with 100 ml. of dry ether and added to the stirred mixture over a period of 35 minutes. The mixture was allowed to warm to room temperature over a period of six hours and then stirred overnight. The mixture was then distilled until its temperature reached 60°, cooled, diluted with ether, and hydrolyzed with ice and dilute hydrochloric acid. The crude product was filtered, washed with water, ether and dried. It was purified by dissolving in 300 ml. of toluene, decolorizing with 10 g. of Norite, followed by evaporation to 150 ml. volume and crystallization. An additional recrystallization from toluene gave 34.7 g. (54.1%) of III, m.p. 186.5–187.5°; $\lambda_{\max.}^{\text{alc.}}$ 223 mμ (*E* 20,950); 241 mμ (*E* 12,900); 332 mμ (*E* 23,800).

Anal. Calcd. for $C_{22}H_{22}O_3$: C, 79.04; H, 6.58. Found: C, 79.06; H, 6.51.

trans,anti(?)**-1-(*p*-Methoxyphenyl)-3-hydroxy-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (V).**—A solution of 3.0 g. of III in 30 ml. of *n*-propanol, 90 ml. of sulfur-free benzene and 1.0 ml. of glacial acetic acid was hydrogenated over 0.5 g. of 30% palladium–charcoal catalyst[17] until gas absorption ceased. Approximately 2 moles of hydrogen was absorbed in eight hours. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was recrystallized twice from boiling acetone to give 2.4 g. (80%) of V, m.p. 191–193°. Treatment with acetic anhydride in pyridine gave an acetate, m.p. 120–121.5°.

Anal. Calcd. for $C_{22}H_{26}O_3$: C, 78.11; H, 7.6. Found: C, 77.88; H, 7.67.

trans,anti(?)**-1-(*p*-Methoxyphenyl)-3-keto-7-methoxy-1,2,-3,4,4a,9,10,10a-octahydrophenanthrene (VI).**—The alcohol V was oxidized to the ketone using the method of Oppenauer[18] with aluminum *t*-butoxide and cyclohexanone producing the crude ketone in 60% yield, m.p. 148–152°. The pure ketone was obtained by forming the semicarbazone, followed by hydrolysis with pyruvic acid in aqueous acetic acid.[19] Two recrystallizations from acetone gave 0.45 g. (45%) of VI, m.p. 154.5–156°.

Anal. Calcd. for $C_{22}H_{24}O_3$: C, 78.57; H, 7.14. Found: C, 78.56; H, 7.13.

From Reduction of III in Alkaline Medium.—A solution of 1.5 g. of III in 70 ml. of sulfur-free benzene was added to a solution of 0.2 g. of potassium hydroxide in 3 ml. of methanol and 60 ml. of *n*-propanol. The mixture was stirred under hydrogen at atmospheric pressure with 0.5 g. of 30% palladium–charcoal catalyst for seven hours. A total of 118 ml. of hydrogen was absorbed corresponding to 1.2 moles. The reaction mixture was treated with 0.3 ml. of 20% hydrochloric acid, filtered and the filtrate concentrated *in vacuo*. The residue was diluted with water, filtered by suction and recrystallized from ethanol. A yield of 1.1 g. (73%) of impure VI was obtained, m.p. 149–155°.

trans,anti(?)**-1-(*p*-Methoxyphenyl)-7-methoxy-1,2,3,4,4a,-9,10,10a-octahydrophenanthrene (VII).**—To a solution of 1.0 g. of sodium in 75 ml. of diethylene glycol was added 2.3 g. of VI and 4.0 g. of hydrazine hydrate. The solution was refluxed 30 minutes in a nitrogen atmosphere. The solution was then heated to 200° in 30 minutes, to 237° in an additional 15 minutes. The solution was then heated at 237-245° for 25 minutes during which time 35 ml. of distillate was collected and 135 ml. of nitrogen was evolved. The solution was then cooled to room temperature, diluted with water, and acidified with dilute hydrochloric acid. The mixture was extracted twice with ether, the combined ether extracts washed twice with water and evaporated *in vacuo*. The residue was remethylated with potassium hydroxide and methyl sulfate and the oil formed taken up in benzene. The benzene layer was washed with water, dried over magnesium sulfate, and evaporated *in vacuo*. The residue was recrystallized twice from acetone to give 1.2 g. of needle crystals, m.p. 133–134.5°; $\lambda_{\max.}^{\text{alc.}}$ 223 mμ (*E* 18,900), 277 mμ (*E* 3880).

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.98; H, 8.0. Found: C, 82.10; H, 8.21.

trans,anti(?)**-1-(*p*-Hydroxyphenyl)-7-hydroxy-1,2,3,4,4a,-9,10,10a-octahydrophenanthrene (VIII).**—A mixture of 1.2 g. of VII, 50 ml. of glacial acetic acid and 50 ml. of 48% hydrobromic acid was refluxed three hours in an argon atmosphere. The mixture was cooled, diluted with water and extracted twice with ether. The combined ether extracts were washed with water, sodium bicarbonate solution, water, saturated brine and dried over magnesium sulfate. The mixture was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in acetone, toluene added, and the solution evaporated until crystallization began. The mixture was allowed to crystallize at room temperature and filtered giving 0.9 g. (82%) of VIII, m.p. 230–232° (vac.).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.92; H, 7.58.

trans(?)**-1-(*p*-Methoxyphenyl)-7-methoxy-1,2,3,9,10,10a-hexahydrophenanthrene (IX) and 1-(*p*-methoxyphenyl)-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (X).**—To 110 ml. of diethylene glycol in a 125-ml. distilling flask was added 7.0 g. of barium hydroxide octahydrate. The mixture was heated in an argon atmosphere until all of the water was driven off and about 10 ml. of the glycol distilled over at 240–245°. After cooling to room temperature, 4.5 g. of anhydrous hydrazine and 4.0 g. of the ketone III were added. The mixture was heated to 200° in 30 minutes, with occasional shaking until solution of III occurred, and then to 234° in 15 minutes. Heating was continued at 235–245°, with slow distillation of the glycol, until the nitrogen evolution slowed to 1 ml. per minute, which generally took about 30 minutes. The reaction mixture was then cooled to room temperature, diluted with water, and extracted twice with ether. The combined ether extracts were washed with dilute acetic acid, 10% sodium hydroxide, water and dried over magnesium sulfate. The mixture was filtered and the filtrate concentrated to a volume of 25 ml.; 15 ml. of absolute ethanol was added and the evaporation continued until a volume of 15 ml. was reached. The product which separated on cooling was filtered, washed free of colored material with alcohol and dried. The crude material was dissolved in benzene, decolorized with three 0.5-g. portions of Norite, and the solution evaporated to dryness *in vacuo*. The residue was recrystallized from acetone giving 1.5 g. (39.2%) of IX, m.p. 118–119°; $\lambda_{\max.}^{\text{alc.}}$ 263.5 mμ (*E* 18,600).

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.50; H, 7.50. Found: C, 82.75; H, 7.52.

The mother liquor from IX was diluted with ether, washed with water, 10% sodium hydroxide, water and evaporated *in vacuo*. The residue was taken up in benzene, boiled to remove water, diluted with 60° naphtha and decolorized repeatedly with Norite until a colorless solution was obtained, which was evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol giving 0.21 g. (5.5%)

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[13] All melting points in this paper are corrected.

[14] G. Stork, THIS JOURNAL, **69**, 576 (1947).

[15] V. C. Burnop, G. H. Elliot and R. P. Linstead, *J. Chem. Soc.* 727 (1940).

[16] E. Schwenk and D. Papa, THIS JOURNAL, **67**, 1432 (1945).

[17] R. P. Linstead and S. L. S. Thomas, *J. Chem. Soc.*, 1127 (1940).

[18] R. V. Oppenauer, *Org. Synthesis*, **21**, 18 (1941).

[19] E. B. Hershberg, *J. Org. Chem.*, **13**, 542 (1948).

of X, m.p. 74–76°. Further purification by adsorption from benzene, naphtha solution on alumina gave a product melting at 77.2–77.8°; $\lambda_{\text{max.}}^{\text{alc.}}$ 275 mμ (*E* 19,100).

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.50; H, 7.50. Found: C, 82.57; H, 7.61.

Attempted Dehydrogenation of IX.—One gram of IX was dissolved in 60 ml. of reagent acetone, and shaken in a nitrogen atmosphere with 0.5 g. of 30% palladium–charcoal catalyst at 90–95° for three hours. The mixture was cooled, filtered, and the filtrate concentrated to a volume of 5 ml. and cooled to yield 0.4 g. of XII, m.p. 150–153°. By concentrating the mother liquors and replacing the acetone with alcohol, an additional 0.3 g. of material was isolated, m.p. 110–125°. Recrystallization failed to raise the melting point, and the product was unchanged by further treatment with palladium–charcoal in acetone.

1-(*p*-Hydroxyphenyl)-7-hydroxy-1,2,3,4,9,10-hexahydrophenanthrene (XI).—To a solution of 4.0 g. of 85% potassium hydroxide in 20 ml. of diethylene glycol was added 1.0 g. of IX. The mixture was heated rapidly to the boiling point and boiled at 245° for 13 minutes in an argon atmosphere, with some distillation occurring. The solution was cooled, diluted with water, acidified with acetic acid and extracted twice with ether. The combined ether extracts were washed with water, sodium bicarbonate solution and dried over magnesium sulfate. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was taken up in benzene and boiled until crystallization ensued. The mixture was then cooled and filtered, giving 0.6 g. of slightly tan product. Crude product totaling 1.7 g. was dissolved in reagent ether and decolorized three times with Norite. Benzene was then added and the solution evaporated *in vacuo* until crystals began to form. The mixture was then diluted with benzene and chilled. The yield of XI was 1.1 g. (42.7% over-all), m.p. 207.5–209° (vac.); $\lambda_{\text{max.}}^{\text{alc.}}$ 275.5 mμ (*E* 20,500).

Anal. Calcd. for $C_{20}H_{20}O_2$: C, 82.18; H, 6.85. Found: C, 82.19; H, 6.68.

Methylation of XI.—To a solution of 0.084 g. of sodium (0.00365 mole) in 6 ml. of dry methanol was added a solution of 0.5 g. of XI (0.00171 mole) in 6 ml. of dry methanol. The mixture was heated at reflux in an argon atmosphere while 0.680 g. of methyl *p*-toluenesulfonate (0.00365 mole) was added with stirring. The solution was refluxed one hour and then evaporated *in vacuo* until sodium *p*-toluenesulfonate separated. The mixture was diluted with water and extracted with ether. The ether solution was washed with dilute potassium hydroxide solution, water and dried over magnesium sulfate. The mixture was filtered and the filtrate evaporated *in vacuo*. The residue was recrystallized from alcohol giving 0.3 g. of product, m.p. 68–72°; mixed melting point with X, 69–76°, indicating that the product is X rather than IX.

cis,anti(?)-**1-(*p*-Methoxyphenyl)-7-methoxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XII).**—A solution of 1.0 g. of IX in 30 ml. of sulfur-free benzene was hydrogenated at atmospheric pressure over 0.5 g. of 30% palladium–charcoal catalyst until gas absorption ceased. Approximately one mole of hydrogen was absorbed in 3.5 hours. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized twice from acetone giving 0.8 g. (80%) of XII, m.p. 152.5–153.5°; $\lambda_{\text{max.}}^{\text{alc.}}$ 224.5 mμ (*E* 20,850); 278 mμ (*E* 4420).

From X.—A solution of 0.15 g. of X in 15 ml. of ethanol, 5 ml. of sulfur-free benzene was stirred overnight with 0.2 g. of 30% palladium–charcoal catalyst under hydrogen at atmospheric pressure. Approximately one mole of hydrogen was absorbed. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from ethanol to give 0.135 g. (90%) of XII, m.p. 151–153°.

From XI.—A solution of 0.15 g. of XI in 20 ml. of ethanol was stirred overnight with 0.2 g. of 30% palladium–charcoal catalyst under hydrogen at atmospheric pressure. Approximately one mole of hydrogen was absorbed, most of it in the first 15 minutes. The mixture was filtered and evaporated to dryness *in vacuo*. The residue was dissolved in 6 ml. of dry methanol, added to a solution of 0.16 g. of sodium in 10 ml. of dry methanol and remethylated by refluxing with 1.4 g. of methyl *p*-toluenesulfonate for two hours in an argon atmosphere. The reaction mixture was evaporated *in vacuo* and the residue diluted with water. The product was filtered by suction and recrystallized twice from ethanol to give 0.08 g. (50%) of XII, m.p. 148–151°; mixed melting point with XII showed no depression, with VII depressed to 120°.

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.98; H, 8.08. Found: C, 81.67; H, 8.27.

cis,anti(?)-**1-(*p*-Hydroxyphenyl)-7-hydroxy-1,2,3,4,4a,9,10,10a-octahydrophenanthrene (XIII).**—A mixture of 1.5 g. of XII, 60 ml. of glacial acetic acid and 60 ml. of 48% hydrobromic acid was refluxed in an argon atmosphere for three hours. The reaction mixture was worked up using the same method as for VIII. The final yield was 1.3 g. (95%) of XIII, m.p. 220.5–222° (vac.).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.71; H, 7.54.

1-(*p*-Methoxyphenyl)-7-methoxy-3,4-dihydrophenanthrene (XIV).—The Grignard reagent from 10.0 g. of *p*-bromoanisole and 2.6 g. of magnesium turnings in 60 ml. of dry ether and 15 ml. of dry benzene was cooled to −10° in an ice–salt mixture, in an argon atmosphere. A solution of 10.0 g. of 1-keto-7-methoxy-1,2,3,4-tetrahydrophenanthrene[20] in 30 ml. of dry ether and 30 ml. of dry benzene was added over a period of 30 minutes with stirring and the mixture allowed to warm to room temperature and stirred an additional five hours. The mixture was allowed to stand overnight and then hydrolyzed with aqueous ammonium chloride. The benzene–ether layer was washed with water, sodium bicarbonate solution, water and dried over magnesium sulfate. The mixture was filtered and the filtrate evaporated *in vacuo*. The residual carbinol was dehydrated by heating with 50 ml. of acetic anhydride at 120° for one hour. The bulk of the acetic anhydride was then removed by vacuum evaporation and the residue treated with water. The resulting suspension was boiled to remove the bulk of the anisole present. The product was filtered, washed with acetone–water solution and dried. The crude product was recrystallized three times from acetone giving 5.9 g. (42.2%) of XIV, m.p. 168–170°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.54; H, 6.33. Found: C, 83.81; H, 6.53.

1-(*p*-Methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydrophenanthrene (XV).—A solution of 5.9 g. of XIV in 60 ml. of sulfur-free benzene and 0.1 ml. of glacial acetic acid was hydrogenated at atmospheric pressure over 0.5 g. of 30% palladium–charcoal catalyst until gas absorption ceased. Approximately one mole of hydrogen was absorbed in 90 minutes. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized twice from acetone giving 5.7 g. (96.6%) of XV, m.p. 123.5–125.5°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 83.02; H, 6.91. Found: C, 83.36; H, 6.72.

1-(*p*-Hydroxyphenyl)-7-hydroxy-1,2,3,4-tetrahydrophenanthrene (XVI).—A mixture of 1.0 g. of XV and 25 g. of pyridine hydrochloride was heated in an argon atmosphere at 193–195° for 2.5 hours. The reaction mixture was cooled, treated with water and extracted twice with ether. The combined ether extracts were washed with water, sodium bicarbonate solution, water and dried over magnesium sulfate. The mixture was filtered and the filtrate evaporated to dryness *in vacuo*. The residue was taken up in benzene and boiled until crystallization ensued. The mixture was cooled and filtered giving 0.74 g. of crude product. The pure phenol was obtained by dissolving the crude product in reagent ether, decolorizing twice with Norite, adding benzene and evaporating *in vacuo* until crystals formed. More benzene was added and the mixture chilled. This recrystallization was repeated once more to give 0.5 g. (55%) of XVI, m.p. 223.5–225 (vac.).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.76; H, 6.21. Found: C, 82.90; H, 6.20.

1-(*p*-Methoxyphenyl)-7-methoxyphenanthrene (XVII) a. From XV.—A mixture of 0.5 g. of XV with 0.10 g. of roll sulfur was heated in a carbon dioxide atmosphere at 170–230°. When the evolution of hydrogen sulfide ceased after 30 minutes, the reaction mixture was cooled and dissolved in alcohol. The solution was boiled with 4 ml. of 20% potassium hydroxide solution for ten minutes to remove any unreacted sulfur and then poured into water.

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(20) G. Stork, THIS JOURNAL, **69**, 2936 (1947).

After separating and drying the crude product, it was dissolved in benzene–60° naphtha solution and decolorized twice with Norite, and the solution evaporated to dryness *in vacuo*. The residue was recrystallized from absolute alcohol–acetone solution to give 0.2 g. of XVII, m.p. 115.2–115.8°.

b. From XII.—Dehydrogenation of 0.7 g. of XII with an equivalent amount of roll sulfur was carried out using the above procedure giving 0.3 g. of XVII identical with that obtained from XV.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.07; H, 5.73. Found: C, 84.24; H, 6.02.

MISSOULA, MONTANA

NOTES

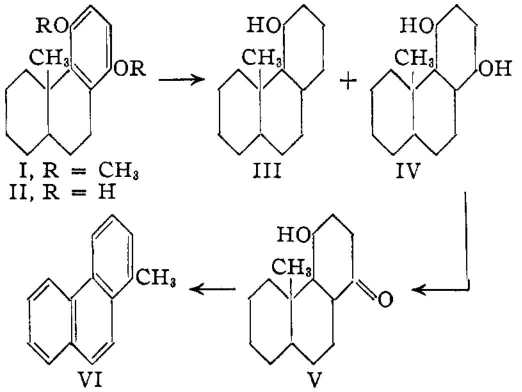
Synthesis of Phenanthrenes. VI. 5-Hydroxy-8-keto-4a-methylperhydrophenanthrene

BY RODERICK A. BARNES AND ALBERT H. SHERMAN[1]

RECEIVED JANUARY 2, 1953

Previous work[2-4] has been directed toward the preparation of octahydrophenanthrenes as possible intermediates for the synthesis of steroids. From such intermediates there are two main paths by which further progress toward the steroids might be achieved. The aromatic C ring may be reduced and then the D ring added or the two procedures might be reversed.

The purpose of this paper is to report some results which have been obtained in connection with the first approach. 5,8-Dimethoxy-4a-methyl-1,2,3,4,-4a,9,10,10a-octahydrophenanthrene (I), which has previously been described,[2] was treated with hydrogen bromide to cleave the methoxyl groups. The resulting hydroquinone (II) was rather unstable toward oxygen particularly in basic solution.

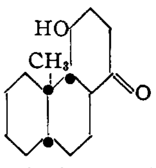


Two reductions of II were carried out; from the first there was isolated one isomer of 5,8-dihydroxy-4a-methylperhydrophenanthrene along with a large amount of unhydrogenated material. The second hydrogenation under more drastic conditions completely reduced the aromatic ring but also caused rather extensive hydrogenolysis. By chromatographic fractionation of the reduction product a single crystalline monohydroxy-4a-methylperhydrophenanthrene (III) and three additional isomers of diol IV were separated.

It is believed that III has the hydroxyl group at the 5-position. This seems likely because the hydrogenolysis requires the close approach of the catalyst surface and the hydroxyl-bearing carbon atom. Such a process would be sterically inhibited at the 5-position by the angular methyl group. Also, when III was oxidized and the resulting ketone treated with methylmagnesium iodide and then dehydrogenated no 4-methylphenanthrene was isolated. It is not surprising that the Grignard reagent would fail to add to the sterically hindered carbonyl group.

The oxidation of diol IV was investigated since most procedures for adding ring D require a keto group at the 8-position. N-Bromosuccinimide in aqueous dioxane oxidized the crude mixture of diols (from second hydrogenation) and after equilibration with base followed by distillation a single ketoalcohol (V) was isolated. It was anticipated that the sterically unhindered hydroxyl group (at the 8-position) would be preferentially oxidized. This was proved by treating V with methylmagnesium iodide and then dehydrogenating the addition product. The formation of 1-methylphenanthrene proved that the keto group of V must have been at carbon 8.

Although the stereochemistry of V has not been established some reasonable assumptions can be made. According to the theoretical considerations previously presented[2] the starting octahydrophenanthrene (II) should have the *cis* configuration of rings A and B.[5] If the results obtained by Cornforth and Robinson[6] in the hydrogenation of a similar *cis*-octahydrophenanthrene can be used as a basis for generalization it seems likely that the hydrogen at carbon 4b is *cis* to the angular methyl group.



Since V was obtained after equilibration with base the *trans* configuration of rings B and C is most probable. There is as yet no evidence bearing on the configuration of the hydroxyl group of V.

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[1] Abstracted from a thesis presented by A. H. Sherman to the Graduate School for the Ph.D. degree, November, 1952.

[2] R. A. Barnes, THIS JOURNAL, **75**, 3004 (1953).

[3] R. A. Barnes and M. D. Konort, *ibid.*, **75**, 303 (1953).

[4] R. A. Barnes, H. P. Hirschler and B. R. Bluestein, *ibid.*, **74**, 4091 (1952).

[5] The experimental verification of this prediction is currently in progress.

[6] J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 1855 (1949).