1-Carboxy-1,2,3,10b-tetrahydrofluoranthene, IV.—A mixture of 50 g. of zinc, 25 cc. of water, 50 cc. of concentrated hydrochloric acid, 35 cc. of toluene, 5 cc. of acetic acid and 2.64 g. of the keto acid III was refluxed four hours, 25 cc. more of concentrated hydrochloric acid added and refluxing continued twenty-nine hours longer with two more additions of fresh hydrochloric acid. The toluene layer was separated, washed successively with acid, water and saturated sodium chloride solution. The toluene solution was filtered and the filtrate extracted with sodium carbonate solution. The alkaline extract was acidified and the precipitate filtered and dried and crystallized from benzene to give 1.89 g. of pure IV, m. p. 166.8-167.4° as a first crop and 0.42 g. of less pure material, m. p. 154-159°. *Anal.* Calcd. for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6. Found: C, 81.9; H, 5.6.

Fluoranthene-1-carboxylic Acid, V.—A mixture of 0.60 g. of IV and 0.154 g. of sulfur was heated at 240° for twenty-five minutes. The melt which solidified on cooling was dissolved in benzene and the benzene solution concentrated to give 0.50 g. of V, yellow needles, m. p. 227-230°. A sample for analysis was crystallized from acetic acid. *Anal.* Calcd. for $C_{17}H_{10}O_2$: C, 82.9; H, 4.1. Found: C, 82.9: H, 3.9

Fluoranthene, VI.—About 20 mg. of V in 2 cc. of dimethylquinoline was refluxed with a pinch of copper powder for about ten minutes. The cooled mixture was taken up in benzene and the benzene solution extracted with acid. The benzene layer was dried and evaporated. The residue was crystallized from alcohol and gave fluoranthene, m. p. 110.4-111.2°; mixed melting point with an authentic sample gave no depression.

Ethyl Fluoranthene-1-carboxylate, VII.—The acid V (1.63 g.) was esterified with ethanol and hydrogen chloride in the usual way. Crystallization from ethanol gave 1.48 g. of the ester VII as tan needles, m. p. 103.2-104.8°. *Anal.* Calcd. for $C_{19}H_{14}O_2$: C, 83.2; H, 5.1. Found: C, 83.1; H, 5.2. The trinitrofluorenone complex was obtained in the usual way[8] and recrystallized from benzene-ethanol to give yellow silky needles, m. p. 140.0-140.4°. *Anal.* Calcd. for $C_{32}H_{19}O_9N_3$: N, 8.0. Found: N, 7.8.

Hydrazide of Fluoranthene-1-carboxylic Acid, VIII.—A mixture of 1.50 g. of the ester VII, 25 cc. of absolute ethanol and 0.7 cc. of hydrazine hydrate was refluxed for seven hours. The solution was concentrated to about 10 cc. and 0.5 cc. more of hydrazine added and refluxing continued an additional sixteen hours. After cooling, the precipitate was filtered to give 1.44 g. of material, m. p. 109-185°. This was recrystallized from benzene to give 0.28 g. of material, m. p. 220-223°. The mother liquor on concentration gave an obvious mixture. It was redissolved in ethanol and the solution treated for fifty hours at reflux with 1 cc. of hydrazine hydrate. After separation of a first crop of hydrazide, the mother liquor was treated once more with hydrazine hydrate. In all, 1.4 g. of the hydrazide, m. p. 224.5-225.5°, was obtained. *Anal.* Calcd. for $C_{17}H_{22}ON_2$: C, 78.4; H, 4.7; N, 10.8. Found: C, 78.2; H, 4.2; N, 11.9. It would probably have been simpler to prepare the hydrazide by using a large excess of hydrazine hydrate originally.

1-Fluoranthenyl Urethan, IX.—To a solution of 1.00 g. of the hydrazide, VIII, in 25 cc. of acetic acid there was added 1 cc. of concentrated hydrochloric acid. The suspension was cooled to 0° with stirring and 0.9 g. of sodium nitrite in 8 cc. of water was added dropwise in the cold with stirring. The mixture was stirred at 0° for one hour, then allowed to come to room temperature. The mixture was diluted with water and filtered. The deep yellow azide was dried in a vacuum desiccator overnight. It melted at 101° with decomposition. It was placed in a flask with 75 cc. absolute ethanol and the mixture warmed gently, then refluxed for three hours. Concentration of the solution gave 0.97 g. of urethan as tan, almost colorless needles, m. p. 171.0-171.8°. *Anal.* Calcd. for $C_{19}H_{15}O_2N$: C, 78.8; H, 5.2. Found: C, 78.6; H, 4.8.

1-Aminofluoranthene, X.—A mixture of 0.82 of the urethan IX, 15 cc. of concentrated hydrochloric acid and 10 cc. of acetic acid was placed in a sealed tube and heated at about 140° for four hours. The tube was cooled in liquid nitrogen and opened. The precipitate was filtered and washed well with water and dried. It weighed 0.70 g. and melted at 234-240°. It was placed in a separatory funnel containing ether-benzene and 10% sodium hydroxide solution. After shaking for about half an hour, the solid phase disappeared. The organic layer was washed well with water and dried. It fluoresced strongly in ordinary light. On concentration, the solution deposited 0.53 g. of yellow needles of **X**, m. p. 133.0-134.0°. *Anal.* Calcd. for $C_{16}H_{11}N$: N, 6.5. Found: N, 7.3. The trinitrofluorenone complex[8] crystallized from benzene as dark brown crystals, m. p. 254-255° (uncor.). *Anal.* Calcd. for $C_{29}H_{16}N_4O_7$: N, 10.4. Found: N, 11.2.

(8) Orchin, Reggel and Woolfolk, THIS JOURNAL, **69**, 1225 (1947).

Summary

A new general synthesis of fluoranthene and its derivatives is reported. The anhydride resulting from the condensation of fluorene and maleic anhydride is cyclized to 1-carboxy-3-keto-1,2,3,10b-tetrahydrofluoranthene which is then reduced and dehydrogenated to fluoranthene-1-carboxylic acid. The carboxyl group is esterified and Curtius degradation of the ester gives 1-aminofluoranthene.

THE DANIEL SIEFF INSTITUTE
REHOVOTH, ISRAEL

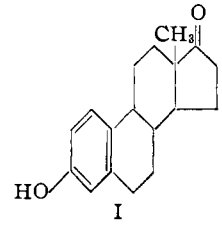
RECEIVED JANUARY 3, 1949

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Synthetic Sterols. II.[1] An Isomer Technique

BY JOHN A. HOGG

As the first of several model studies directed toward a scheme for the total synthesis[2] of estrone (I), the preparation of 1,2-dimethyl-7-methoxy-1,-2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (IIIα, β) was described in the first paper of this series.[1]



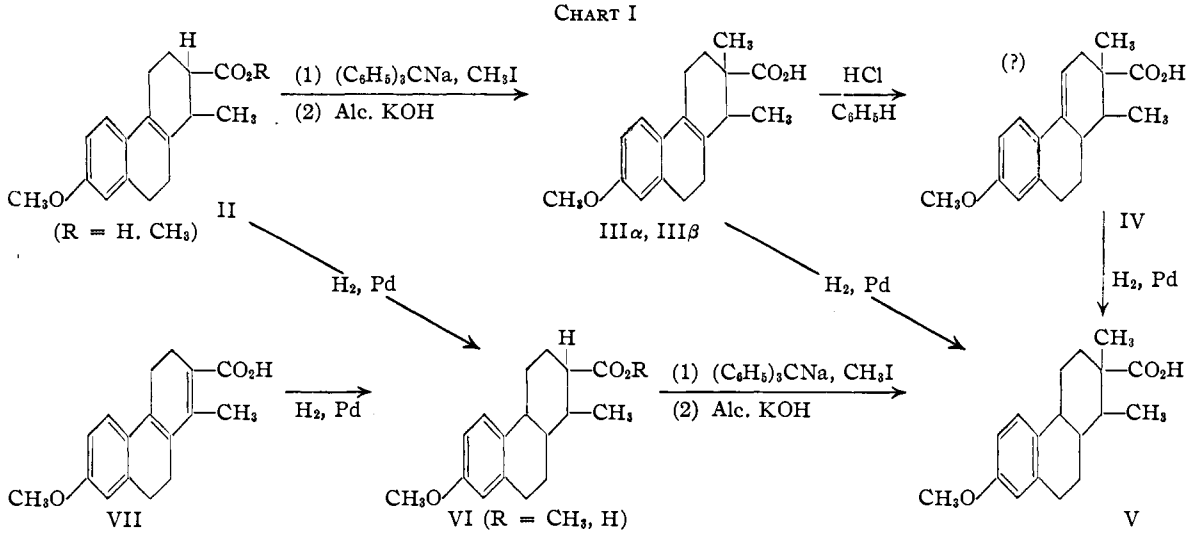
I

The structure assigned to estrone (I) is capable of sixteen stereochemical variations (eight diastere-

(1) Previous paper: Hogg, THIS JOURNAL, **70**, 161 (1948).

(2) The total synthesis of estrone was recently achieved by Anner and Miescher [see *Experientia*, **3**, 279 (1947), and *Helv. Chim. Acta*, **31**, 2173 (1948)] through a unique variation of the splendid scheme used by Bachmann, Kushner and Stevenson, THIS JOURNAL, **64**, 974 (1942), in their synthesis of estrone-a, an isomer of estrone.

CHART I



oisomers); therefore, in the choice of a scheme for its synthesis, it is important that provision be made for the controlled introduction of the asymmetric centers in order to favor the isolation of a large number of isomers.

Since the stereochemical possibilities of estrone are duplicated by 1,2-dimethyl-7-methoxy-1,2,3,-4,9,10,11,12 - octahydrophenanthrene - 2 - carboxylic acid (V), a systematic study was undertaken to prepare the latter by methods in which the number of asymmetric centers introduced in each operation, as well as the sequence of introduction, were varied.

Seven of the eight theoretically possible diastereoisomers of V were obtained. The details of this work are reported in the present paper.

The materials utilized for the synthesis of V are the unsaturated acids (II, IIIα, IIIβ and VII) which were reported in paper I.[1] The following methods were employed.

Method I. The Introduction of Asymmetric Centers in Pairs.—Compounds IIIα and IIIβ already have two asymmetric centers present. The formation of four racemates is theoretically possible in the hydrogenation of either IIIα or IIIβ.

By the direct hydrogenation of IIIα in the presence of palladium-on-Norite two forms of V were obtained. The separation of these two isomers was accomplished by triturating the crude reduction product with an aqueous sodium hydroxide solution adjusted in concentration and amount so that partial solution of the salts occurred. Regeneration of the acid from the insoluble salt yielded a product melting at 192–194° (Va) after recrystallization from ethyl alcohol. The aqueous alkaline filtrate yielded, after acidification and purification by crystallization from ethyl alcohol, an acid of m. p. 178–180° (Vb).

A similar result was obtained by the hydrogenation of IIIβ. In this case the alkali salts did not exhibit the useful difference in solubility. However, by careful fractionation two new isomers melting at 176–178° (Vc) and 225–226° (Vd) were obtained.

Method II. Angular Methylation after Hydrogenation of II (R = H) and VII.—It appeared possible that different isomers of V might be produced by introducing the angular methyl group after complete saturation with hydrogen of the double bonds in I and IV. The hydrogenations resulted in one and the same form of VI (R = H) of m. p. 128° in good yields in each case. Diazomethane and VI (R = H) produced an oil (VI, R = CH_3). When the latter was treated with triphenylmethyl sodium and methyl iodide with subsequent hydrolysis in alcoholic potassium hydroxide over a ten-hour period, less than 10% of the crude ester was saponified. This more than usual resistance to mild alkaline hydrolysis proved to be a new and useful means for separating isomers, for the acid thus obtained was a new isomer (Ve) of m. p. 208–210°. The unreacted ester proved to be a nearly pure racemate, for saponification under reflux in ethylene glycol with potassium hydroxide yielded an acid of high purity and in high yield, m. p. 192–194°. This isomer was identified with that isomer (Va) of the same melting point obtained from IIIα by method I.

Method III. Isomerization of the Double Bond before Hydrogenation.[3]—By treating IIIα (m. p. 206–208°) with dry hydrogen chloride in benzene solution a change occurred in the molecule as was indicated by the depression of the melting point to 150–165°. A test for chlorine was negative. Almost the entire product formed a difficultly soluble potassium salt, and purification by fractional crystallization was difficult. Hence the entire crude material was hydrogenated in the presence of palladium and diethylamine. This choice of procedure eliminates the need for isolating the isomeric form which may possibly revert

(3) The isomerization and subsequent hydrogenation of the double bond in IIIβ was omitted in this work.

to the original form (IIIα) under the conditions of purification. From this crude hydrogenation mixture there were obtained three isomers of V, m. p. 172–174° (Vg), 185–187° (Vf), and 178–180° (Vb, identical with the isomer of the same melting point obtained from IIIα in Method I).

Compound Va was not altered by treatment with dry hydrogen chloride in benzene under the same conditions that brought about a change in IIIα, indicating that demethylation does not occur under these conditions.

TABLE I

Compound	M. p., °C.	Estrogenic activity, γ	U. V. absorption max.
II (R = H)	193–195	20.00	272
IIIα	206–208	0.25	272
IIIβ	172–173	5.00	...
VI (R = H)	128–130	21.70	280
Va	192–194	0.73	278
Vb	178–180	1.50	280
Vc	176–178	...	...
Vd	225–226	...	...
Ve	208–210	6.17	...
Vf	185–187	20.00	278
Vg	172–174	11.70	280
6-Methoxy tetralin	.....	...	280
α-Naphthyl methyl ether	.....	...	233, 261, 271, 314

In the cases where the melting points of the various forms of V were sufficiently close to suggest identity (Vb, c, f, g) all possible mixed melting points showed a depression. A further indication of the dissimilarity of these isomers is observed in the wide variation of estrogenic activity[4] (Table I).

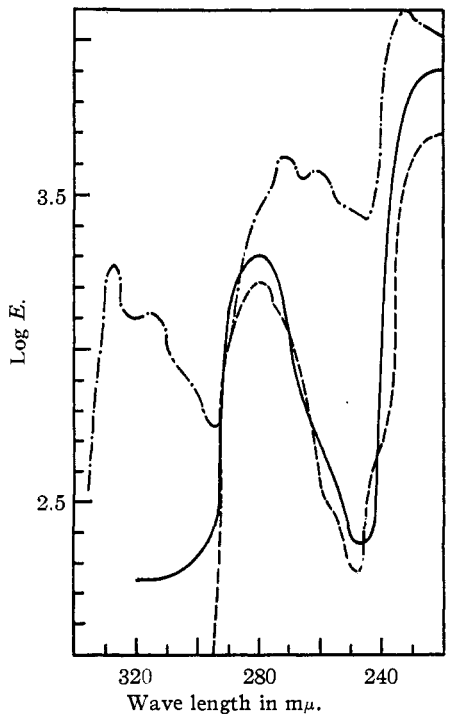


Fig. 1.—Va, ——; β-Naphthyl methyl ether, —·—; 6-methoxytetralin, — — —.

As a check against the possibility of partial aromatization by dehydrogenation, the ultraviolet absorption curves of the products of formula V were determined and compared with the curves obtained from methoxytetralin and β-naphthyl methyl ether (see Fig. 1). Since the curves for all the compounds of structure V examined were nearly identical, only one curve (Va) is shown in Fig. 1. The maxima, recorded in Table I, support the authenticity of the structures assigned.

Observation should be made of the fact that an alternative procedure exists.

The eight theoretically possible racemates of V (seven of which were obtained by the above techniques) require eight resolutions in order to obtain the corresponding set of sixteen enantiomorphs. However, the total number of resolutions required would be reduced if the intermediates (II, IIIα, IIIβ and VII) were first resolved and then converted to V.

Several attempts to resolve IIIα with the optically active alkaloid bases (brucine, quinine, cinchonine and cinchonidine) were unsuccessful due to the formation of unstable salts or stable double salts.

Experimental[5]

Hydrogenation of 1,2-Dimethyl-7-methoxy-1,2,3,4,9,-10-hexahydrophenanthrene-2-carboxylic Acid (IIIα).—Compound IIIα (4.2 g. or 0.0147 mole) in methanol (100 cc.) absorbed the theoretical amount of hydrogen in two hours by shaking at 40 lb. pressure in the presence of 0.5 g. of palladium–Norite catalyst.[6]

After removal of the catalyst and solvent, the crude product was found to melt at 120–130°. This material was triturated with 400 cc. of 1% aqueous sodium hydroxide, whereupon an insoluble sodium salt remained in suspension (2.7 g. after filtration).

When the mother liquor was acidified 1.15 g. of an acid melting at 155–165° was precipitated. Two crystallizations from ethyl alcohol yielded 0.7 g. of thick needles melting at 192–194° (Va).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33. Found: C, 74.84; H, 8.29.

The above-mentioned sodium salt was dissolved with difficulty in a boiling mixture of ethanol and water. The solution was acidified with concentrated hydrochloric acid, thus precipitating an oil which solidified while still hot. By careful crystallization from ethyl alcohol some of the acid melting at 193–195° (Va) was obtained, then the bulk of the product (1.3 g.) melting at 165–170° was deposited in the form of chunky prisms. A final crystallization from the same solvent raised the melting point to 178–180° (Vb).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33. Found: C, 74.92; H, 8.23.

Hydrogenation of IIIβ.—This reaction was carried out in a manner identical with that employed in the hydrogenation of IIIα. From 90 mg. of IIIβ there was obtained a crude product which dissolved readily in a small volume

(4) The estrogenic assays were carried out by Stanley C. Lyster of the Department of Pharmacology and Endocrinology, The Upjohn Company.

(5) All melting points are uncorrected.

(6) Hartung, THIS JOURNAL, **50**, 3370 (1928).

of dilute alkali. Hence, it was necessary to separate the isomers by fractional crystallization. Ethanol–water combinations were used as solvent. Small amounts of two new forms of V were obtained. One of these products melted at 176–178° (Vc) and was found to be different by the mixed melting point method from Va (m. p. 178–180°) obtained from IIIα.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33. Found: C, 75.18; H, 8.34.

The second new isomer melted at 225–226° (Vd), but was obtained in insufficient quantity for satisfactory analysis.

Hydrogenation of 1-Methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic Acid (II, R = H).—One millimole (272 mg.) of II (R = H) was hydrogenated as in the preceding preparations to yield, after crystallization from aqueous ethanol, 200 mg. of 1-methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylic acid (VI, R = H). This material formed fine needles (m. p. 128–130°) when recrystallized rapidly from dilute ethyl alcohol and large prisms (m. p. 134–135°) when recrystallized slowly from ethyl alcohol. The higher melting crystals formed needles melting at 128–130° when recrystallized from dilute ethyl alcohol.

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.50; H, 8.03. Found: C, 74.12; H, 7.75.

Hydrogenation of 1-Methyl-7-methoxy-2,3,9,10-tetrahydrophenanthrene-2-carboxylic Acid (VII).—This hydrogenation was carried out as usual with 10 g. (0.037 mole) of VII. These was obtained, after recrystallization from dilute ethanol, 8.3 g. (82%) of fine needles identical with the product from the previous experiment, m. p. 128–130° and mixed m. p. 128–130°.

Methyl 1-Methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylate (VI, R = CH_3).—This ester was obtained in quantitative yield by the esterification of 6 g. (0.0218 mole) of VI (R = H) with ethereal diazomethane. This ester was an oil, and was used in the next experiment without further purification.

Angular Methylation of Methyl 1-Methyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylate (VI, R = CH_3).—To a dry ethereal (175 cc.) solution of 5.6 g. (0.0195 mole) of VI (R = CH_3) in a glass-stoppered Erlenmeyer flask was added 0.0195 mole of triphenylmethyl sodium in 125 cc. of ether. At the end of three hours, when the red color of the triphenylmethyl sodium had disappeared, an excess of methyl iodide was added. The reaction proceeded rapidly, precipitating sodium iodide at once. Some heat was evolved.

After filtering from the salt the solvent was removed, and the resulting mixture of triphenylmethane and crude product was refluxed for fourteen hours in 200 cc. of 5% alcoholic potassium hydroxide. The alcohol was removed under reduced pressure, and water added. The neutral material was extracted with ether. When acidified the alkaline aqueous layer deposited only 0.3 g. of an acid melting at 145–185°. After two recrystallizations from ethanol the product melted at 208–210°. This new isomer is designated as Ve.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33. Found: C, 74.51; H, 7.98.

The neutral fraction recovered from the above ether extraction was subjected to more drastic saponification by refluxing for twenty-four hours in 200 cc. of a 5% solution of potassium hydroxide in ethylene glycol. Part of the solvent was removed under reduced pressure, and the remaining solution was diluted with a large volume of water. The triphenylmethane was removed by extraction with ether. The aqueous layer was acidified to yield 3.5 g. of nearly pure material melting, after one recrystallization from ethyl alcohol, at 192–194°. This acid was identical with that product (Va) of the same melting point obtained in the hydrogenation of IIIα (Method I).

Isomerization and Hydrogenation of IIIα.—A current of dry hydrogen chloride gas was passed into a solution of 175 mg. of IIIα in dry benzene for one hour. This saturated solution was allowed to stand overnight at room temperature, and then the solvent was removed. The residue solidified and was found to melt at 150–165° (whereas IIIα melts at 206–208°).

Some observations on the behavior of this crude mixture in another experiment indicated the possibility that the unknown form of isomerization undergoes reversion to its original form (IIIα). Therefore, the hydrogenation of the mixture melting at 150–165° was effected directly with the expectation that new isomers of V would result.

When this hydrogenation was carried out in neutral alcoholic solution with palladium-on-Norite as catalyst the only products isolated were those obtained by the direct hydrogenation of IIIα.

However, in another experiment a few drops of diethylamine were added. After removal of the solvent and catalyst, the residue was triturated with 15 cc. of water containing 0.2 g. of potassium hydroxide. Nearly the entire mixture formed an insoluble salt. The acids were regenerated and dissolved in ethyl alcohol. The first crop of crystals (large plates), after one further purification from the same solvent, melted at 172–174° (Vg). A mixed melting point with Va showed depression.

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 75.00; H, 8.33. Found: C, 74.81; H, 7.98.

By concentrating the mother liquor and cooling, a quantity of prisms formed which melted at 178–180° after recrystallization from ethyl alcohol. This acid was identical with Vb.

The mother liquor was then diluted with water. Upon standing, a small amount of very thin broad needles formed which melted at 185–187° (Vf) after another recrystallization from dilute ethyl alcohol. Mixed melting points with Vb, Vc and Vg were depressed.

The quantity obtained was insufficient for satisfactory analysis.

Summary

Various chemical transformations with 1-methyl-7-methoxy-3,4,9,10-tetrahydrophenanthrene-2-carboxylic acid (VII), 1-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (II), and 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (IIIα, IIIβ) have resulted in the formation of seven of the eight possible diastereoisomeric forms of 1,2-dimethyl-7-methoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene-2-carboxylic acid (V).

KALAMAZOO, MICHIGAN RECEIVED AUGUST 18, 1948