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Synthetic Sterols. I. Model Experiments Employing Hagemann's Ester

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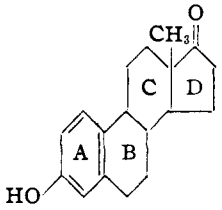
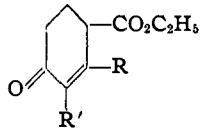
The procedure herein reported has been designed and carried out with the view of obtaining a new and somewhat general method of constructing the molecular framework of estrone (I). A special advantage of the method is that the four asymmetric centers present in octahydrophenanthrene compounds of the estrone type may be introduced in pairs in such a way that the isomer problem is simplified.



(I)



(II)

Hagemann's ester[1] (3-methyl-4-carboethoxycyclohexene-2-one-1 or II, R = CH_3 and R′ = H) has been prepared by Bergmann and Weizmann,[2] and by Smith and Rouault,[3] by the condensation of formaldehyde with ethyl acetoacetate in the presence of piperidine with subsequent selective decarboethoxylation by heating with sodium ethoxide. Conclusive experiments[4] have shown that the alkylation of Hagemann's ester with alkyl halides and sodium ethoxide involves the 2-position.

When this fundamental reaction was applied in this work using *m*-methoxyphenethyl bromide[5] as the alkylating agent with sodium ethoxide in anhydrous ethanol, the yields were unsatisfactory due to extensive alcoholysis. 3-Methyl-2-(*m*-methoxyphenethyl)-4-carboethoxycyclohexene-2-one-1 (III) was, however, prepared in 58% yield by the use of sodamide as the basic catalyst in liquid ammonia. When hydrogenated at two atmospheres using a Pd–Norite catalyst, III absorbed an equivalent amount of hydrogen to give IV which was cyclized with concentrated sulfuric acid without further purification. A 65% over-all yield of crude V was obtained after hydrolysis with alcoholic potassium hydroxide.

The structure of V was confirmed by selenium dehydrogenation to 1-methyl-7-methoxyphenanthrene (XIII). The picrate of the latter was prepared. The acid (V) was converted into its methyl ester (VI) with diazomethane.

(1) Hagemann, *Ber.*, **26**, 876 (1893).
(2) Bergmann and Weizmann, *J. Org. Chem.*, **4**, 267 (1939).
(3) Smith and Rouault, THIS JOURNAL, **65**, 631 (1943).
(4) (a) Kötz, Blendermann, Mahnert and Rosenbusch, *Ann.*, **400**, 77 (1913); (b) Kötz and Auger, *Ber.*, **44**, 466 (1911); (c) Rabe and Pollack, *ibid.*, **45**, 2926 (1912).
(5) Hunter and Hogg, THIS JOURNAL, **68**, 1676 (1946).

Since Hudson and Hauser[6] were successful in the use of triphenylmethylsodium and alkyl halides for the alkylation of simple ethyl dialkylacetates, VI was subjected to a similar treatment. The characteristic wine-red color of triphenylmethyl sodium was found to disappear in an hour's time, whereupon treatment with methyl iodide produced a vigorous reaction. The hydrolysis of the resulting mixture of geometrical isomers in alcoholic potassium hydroxide required prolonged refluxing. The two forms of 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid (VII α, β) were easily separated since their sparingly soluble potassium salts differed in water solubility. One of them, which is regarded as the β (or *cis*) form, was present in small amounts and appeared after acidification of the aqueous alkaline filtrate. The α-form was obtained in 80% yield while only 2% of the β-form was obtained.

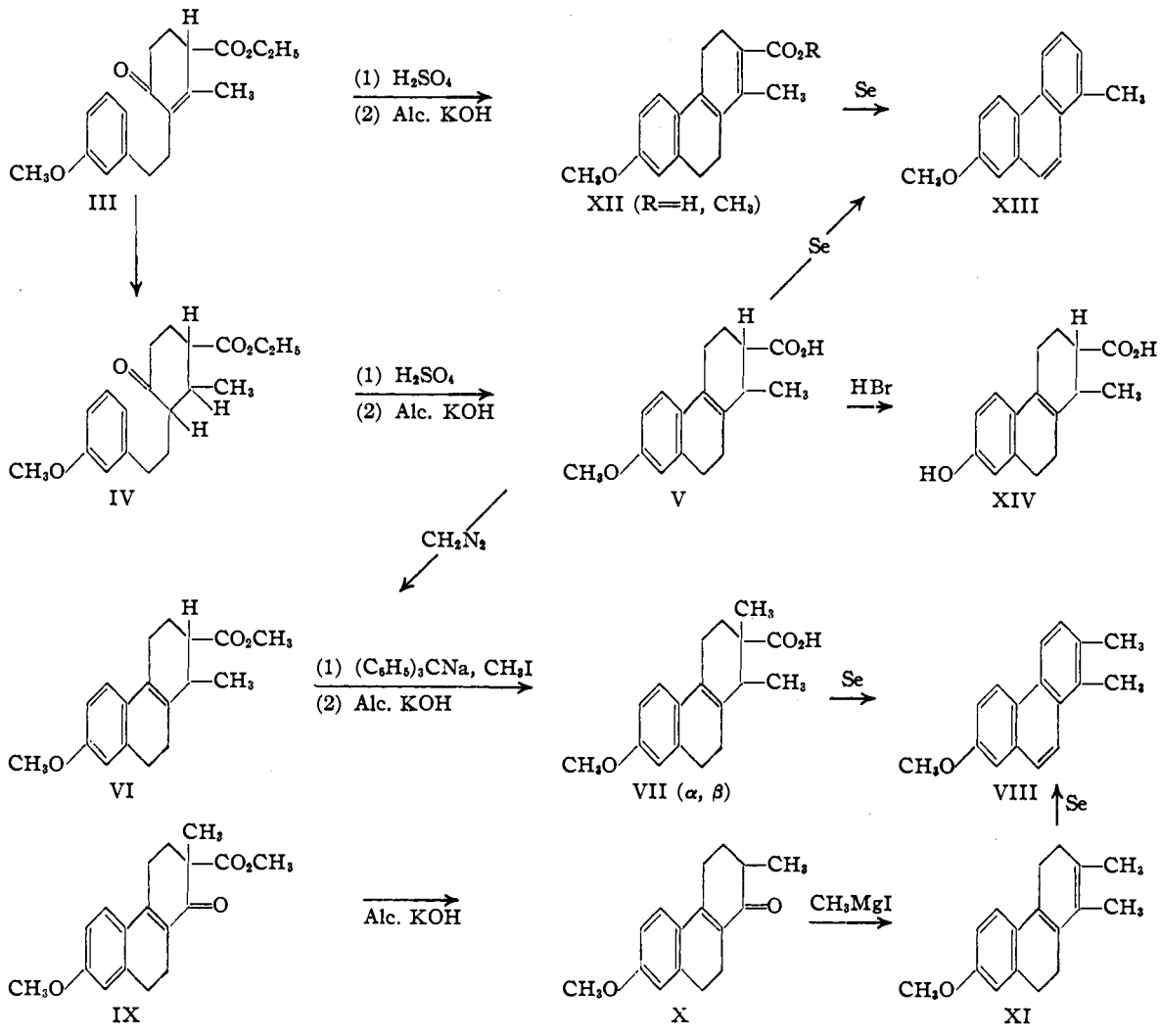
The α-form of VII was heated at 350° with selenium powder to yield 1,2-dimethyl-7-methoxyphenanthrene (VIII). This was confirmed by comparison with an authentic sample prepared from 1-keto-2-methyl-2-carbomethoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (IX).[5,7] The latter was hydrolyzed to X[7] and treated with an equivalent of methylmagnesium iodide. The resulting crude product (XI) was dehydrogenated with selenium to give VIII.

The cyclization of III was also effected directly with concentrated sulfuric acid to give, after hydrolysis, a yellow acid, 1-methyl-7-methoxy-3,4,-9,10-tetrahydrophenanthrene-2-carboxylic acid (XII, R = H), which readily decomposed at its melting point and was best purified through its methyl ester (XII, R = CH_3). This yellow acid is probably of the structure indicated because its color and instability are best accounted for by conjugation. Selenium dehydrogenation of XII (R = CH_3). Selenium dehydrogenation of XII (R = H) resulted in 1-methyl-7-methoxyphenanthrene. The picrate of this phenanthrene derivative showed no depression in melting point when mixed with the picrate of that obtained from V by an identical procedure.

The original investigation of the condensation of ethyl acetoacetate with aldehydes under the influence of basic catalysts was first carried out by Knoevenagel and Klages.[8] Horning, Denekas and Field[9] have extended the work of the latter investigators so that the preparation of 5-substituted

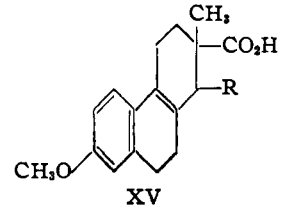
(6) Hudson and Hauser, *ibid.*, **62**, 2457–2459 (1940).
(7) Bachmann, Kushner and Stevenson, *ibid.*, **64**, 974 (1942).
(8) Knoevenagel and Klages, *Ann.*, **281**, 94 (1894).
(9) Horning, Denekas and Field, *J. Org. Chem.*, **9**, 547 (1944).

CHART I



"Hagemann esters" is easily carried out. Mannich and Fourneau[10] have prepared Hagemann's ester by the condensation of 1-diethylaminobutanone-3 with ethyl acetoacetate in the presence of sodium ethoxide. Other β-keto esters would be expected to yield compounds of type II (R′ = H and R variable) under similar circumstances. The variable nature of the products which may be synthesized by the method outlined in Chart I becomes apparent.

The two asymmetric centers present in the geometric isomers VII α and VII β correspond to those between the C and D rings of estrone (I). The resolution of VII α and VII β into their respective optical antipodes would result in a total of four stereoisomers (*d*-VII α, *l*-VII α, *d*-VII β and *l*-VII β). By the hydrogenation of the double bond, one would theoretically expect to obtain from each of these four isomers four additional diastereoisomeric compounds, or a total of sixteen forms which correspond to the sixteen theoretical isomers of the estrone molecule. In a procedure of this sort, the number of chemical species present for separation in any single operation is reduced to a minimum. The method may be regarded as applicable to a systematic approach to the difficult stereoisomeric problem associated with the synthesis of estrone (I). The synthesis of a compound of type XV for this purpose would follow the preparation of a material of type II, where R is of a nature chosen to facilitate the construction of the D ring of estrone. Work along these lines is now in progress.



(10) Mannich and Fourneau, *Ber.*, **71**, 2090 (1938).

The following table (I) records the dosage required to bring about an estrous response in the rat when bioassayed subcutaneously by the Kahnt–Doisy method.

TABLE I

Compound	M. p., °C.	Activity (γ)
V	192–193	22.5
VIIα	206–207	0.24
VIIβ	172–173	5.1
XII (R = H)	192–195 (dec.)	56
XIV	.....	20
Estrone		1.0

Experimental

3-Methyl-2-(*m*-methoxyphenethyl)-4-carboethoxycyclohexene-2-one-1 (III).—To 250 cc. of liquid ammonia containing 0.2 g. of hydrated ferric nitrate was added 13 g. (0.563 mole) of sodium in a piecewise manner with cooling only when necessary to facilitate the speed of addition. The mixture was stirred until the blue color was replaced by gray. The resulting suspension was cooled in an alcohol–Dry Ice-bath, and 102.5 g. (0.563 mole) of Hagemann's ester was added as rapidly as possible with the continued application of the cooling bath. The deep-red reaction mixture was stirred without cooling for twenty minutes and was then cooled again while 300 cc. of dry toluene and 50 cc. of sodium-dried ether were added. The cooling bath was removed and the mixture was stirred two hours at room temperature until nearly all of the ammonia had escaped. Then the reaction vessel was heated to boiling, whence the sodio derivative appeared as a yellow precipitate (some reddish gummy material collected on the sides).

One hundred and twenty grams (0.563 mole) of *m*-methoxyphenethyl bromide was added and the suspension was refluxed under a nitrogen atmosphere for eighteen hours. The resulting mixture was washed with dilute hydrochloric acid and then with water. The toluene layer was dried over magnesium sulfate, and the toluene was removed under reduced pressure. After a small forerun, distillation of the residue yielded 102 g. (58%) of III boiling at 180–184° (0.3 mm.).

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.2; H, 7.58. Found: C, 71.6; H, 7.41.

1-Methyl-2-carboxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (V) from Reduction and Cyclization of III.—Thirty-three grams (0.104 mole) of III in 100 cc. of 95% ethanol was hydrogenated at 35 lb. pressure using 4 g. of palladium–Norite catalyst.[11] The theoretical amount of hydrogen was absorbed in forty-five minutes. After filtration and removal of the solvent there remained a water-white oil of fruity odor. This oil was cooled to −20° in an alcohol–Dry Ice-bath, and to this was added 80 cc. of concentrated sulfuric acid which had been similarly cooled. The viscous content of the flask was stirred with a thermometer as the temperature was allowed to rise slowly. It was necessary to apply cooling from time to time. At no time was the temperature allowed to rise above 10°. After twenty minutes of shaking and stirring, the temperature was allowed to rise to 20°, and the mixture was then poured on a large excess of cracked ice (total reaction time was thirty minutes). A light-colored gum formed which was extracted with ether. The ether was removed, and the residue was hydrolyzed by refluxing for one hour in 200 cc. of a 6% solution of potassium hydroxide in 95% ethanol and 20 cc. of water. The alcohol was then removed under vacuum and diluted with water. The water solution was washed with ether and then acidified with concentrated hydrochloric acid. The acid came out as an oil and quickly solidified. There was obtained 18.5 g. (65%) of crude acid which melted at 174–178°. Two recrystallizations from 95% ethanol raised the melting point to 192–193°. The over-all yield of pure V was 14.2 g. or 50% of the theoretical.

Anal. Calcd. for $C_{17}H_{20}O_3$: C, 75.00; H, 7.35. Found: C, 74.95; H, 7.25.

One attempt to demethylate V with 48% hydrobromic acid yielded an oil, presumably (XIV).

Methyl 1-Methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylate.—A solution of 7.5 g. of V in ether was treated with an excess of ethereal diazomethane. The solvent was removed, and the residue was recrystallized from 95% ethanol to yield 7.3 g. (93%) of VI as plates melting at 107–108°.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.60; H, 7.68. Found: C, 75.61; H, 7.71.

1-Methyl-7-methoxyphenanthrene (XIII) from the Selenium Dehydrogenation of V.—One gram of V was heated for three hours with 6 g. of selenium powder at 350°. The reaction was carried out in a 50-cc. round-bottom flask turned at a 45° angle, with an outlet tube containing a restriction placed inside the flask and sealed with a movable glass bead. The outlet tube and flask were equipped with standard taper joints. The bead permitted the escape of hydrogen selenide and carbon dioxide without distillation of the product through the outlet. When the product collected on the upper sides of the reaction vessel the contact with selenium metal was renewed by rotating the flask.

The product was extracted with chloroform, filtered and the solvent was removed. The solid residue (0.7 g.) was distilled in vacuum over sodium to yield 0.5 g. of a white solid melting at 120–124°. Several recrystallizations of part of this from 95% ethanol raised the melting point to 132–133°. The reported melting point of 1-methyl-7-methoxyphenanthrene (XIII)[12] is 133–134°.

Purification was more easily effected through its picrate. The remainder of the crude product and mother liquors was treated with 25 cc. of a saturated alcoholic solution of picric acid. On cooling, orange needles developed which melted at 138–139° after one recrystallization from 95% ethanol.

Anal. Calcd. for $C_{22}H_{17}O_8N_3$: C, 58.70; H, 3.75; N, 9.32. Found: C, 58.70; H, 3.88; N, 9.39.

1-Methyl-2-carboxy-7-methoxy-3,4,9,10-tetrahydrophenanthrene (XII, R = H) from the Cyclization of III.—To 10 g. of III cooled in an Erlenmeyer flask to −20°, was added 30 cc. of concentrated sulfuric acid also cooled to near its freezing point. The temperature was maintained at or below 10° until the main reaction had ceased, and the temperature was then allowed to rise to 20° as in the cyclization of IV. The contents of the flask were poured into a beaker of cracked ice, and the resulting gum was extracted with ether. After the removal of the ether the residue was hydrolyzed in 100 cc. of 10% alcoholic potassium hydroxide. The solvent was removed in vacuum, and the residue was diluted with water. After one extraction with ether the aqueous solution was acidified with dilute hydrochloric acid. There was formed 5.0 g. (58.5%) of a yellow product which melted at 175–188° with evolution of carbon dioxide. The material was further purified by recrystallization from acetic acid with considerable loss due to decomposition. The acid is soluble in 95% ethanol only with difficulty. The pure product melts at 192–195° (dec.).

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.60; H, 6.67. Found: C, 75.62; H, 6.65.

The methyl ester (XII, R = CH_3) was obtained by treating the acid with ethereal diazomethane. The ester melts at 112–113°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.10; H, 7.05. Found: C, 75.32; H, 7.09.

1-Methyl-7-methoxyphenanthrene (XIII) from the Selenium Dehydrogenation of XII (R = H).—One-half gram of XII (R = H) was heated at 300° for six hours in an open tube with 2 g. of selenium powder. The product

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

(12) Short and Stromberg, *J. Chem. Soc.*, 516–520 (1937).

was extracted with chloroform. The solvent was removed and the residue was distilled under vacuum from sodium. After solution in ethanol and the addition of a saturated ethanolic picric acid solution, an orange picrate was deposited which melted at 138–139°. A mixed melting point with the picrate obtained from the product obtained in the selenium dehydrogenation of V was not depressed.

The Angular Methylation of 1-Methyl-2-carbomethoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VI).—A solution of triphenylmethyl sodium was prepared in ether and titrated according to the directions of Renfrow and Hauser.[13] An equivalent amount (0.0255 mole) of triphenylmethyl sodium was added to an ether solution of 7.3 g. (0.0255 mole) of VI in 300 cc. of sodium-dried ether in a 500-cc. glass-stoppered Erlenmeyer flask. All operations were carried out under an atmosphere of dry nitrogen.

The deep, wine-colored solution was allowed to stand at room temperature with occasional shaking for one hour, at which time the red color had faded to a light orange.

The addition of 25 cc. of methyl iodide caused the ether to reflux, and a copious precipitate of sodium iodide soon developed. After standing overnight the ether was removed, and the residue was refluxed eight hours with 10 g. of potassium hydroxide, 10 cc. of water and 200 cc. of 95% ethanol. The alcohol was removed under vacuum on the steam-bath, and the residue was diluted with water. The potassium salt was insoluble in water at ordinary temperature. Filtration gave a mixture of triphenylmethane and the salt. The filtrate was saved. Several washings with ether removed the triphenylmethane, leaving the white crystalline salt, which weighed 7 g., and represents a yield of 85% in the form of the salt. The latter was dissolved in 250 cc. of boiling water containing enough alcohol to effect solution. Acidification while hot with hydrochloric acid yielded nearly the theoretical amount of acid melting at 197–201° (softens at 190°). Recrystallization from 95% ethanol yielded 5.8 g. (80%) of needles in bundles melting at 206–207°. This compound is 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid.

Anal. Calcd. for $C_{18}H_{22}O_3$: C, 75.60; H, 7.68. Found: C, 75.88; H, 7.79.

The aqueous alkaline filtrate was acidified with hydrochloric acid to give 1.0 g. of a tacky solid which was dissolved in 25 cc. of 95% ethanol. After standing for two days, 150 mg. of beautiful prisms formed which melted at 171–173° with previous softening at 167°. One further crystallization from the same solvent raised the melting point to 172–173°. This product is regarded as the β (or *cis*) form of VII. *Anal.* Calcd. for $C_{18}H_{22}O_3$: C, 75.60; H, 7.68. Found: C, 75.61; H, 7.98.

1,2-Dimethyl-7-methoxyphenanthrene (VIII) from 1,2-Dimethyl-2-carboxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene (VII α).—One gram of VII α was treated with 7 g. of selenium metal in the same manner as V. After distillation from sodium under vacuum there was obtained 0.5 g. of a solid material melting at 120–125°. Several recrystallizations from methanol yielded prisms of 1,2-dimethyl-7-methoxyphenanthrene (VIII) melting at 154–155°. 1,2-Dimethyl-7-methoxyphenanthrene[14] is reported to melt at 154–155°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.70; H, 6.73. Found: C, 86.61; H, 6.94.

The melting point of this material when mixed with an authentic sample of 1,2-dimethyl-7-methoxyphenanthrene, as prepared in the following experiment, was 154–155°.

(13) Renfrow and Hauser, "Organic Synthesis," Vol. XIX, John Wiley and Sons, Inc., New York, N. Y., 1939, p. 83.

(14) Haworth and Sheldrick, *J. Chem. Soc.*, 864 (1934).

Synthesis of 1,2-Dimethyl-7-methoxyphenanthrene (VIII).—1-Keto-2-methyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene[7] (X, m. p. 66–67°) was prepared by the alcoholic alkaline hydrolysis of 1-keto-2-methyl-2-carboethoxy-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene[6,7] (IX) in 63% yield.

To a solution of X (1 g.) in sodium-dried ether was added an excess of methylmagnesium iodide. The Grignard addition product was hydrolyzed with dilute sulfuric acid. The ether layer was separated, washed with water, and dried over magnesium sulfate. The solvent was removed, and the crude residue, which solidified readily, was heated four hours at 350° with 2 g. of selenium powder. After extraction with chloroform and distillation from sodium there was obtained 0.5 g. of a solid material which melted at 130–140°. After several recrystallizations from methanol there were obtained prisms of 1,2-dimethyl-7-methoxyphenanthrene melting at 154–155°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.70; H, 6.73. Found: C, 86.80; H, 6.89.

This product was shown to be identical with that obtained in the previous experiment by the method of mixed melting points.

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Summary

Model experiments have been successfully completed which offer several advances in the problems associated with the synthesis of estrone and estrogenic substances:

1. A new method for the synthesis of the hydrophenanthrene portion of the estrone molecule has been developed. The method lends itself well to further development of the D-ring.

2. The procedure includes a method of introducing the angular methyl group ultimately required in sterol synthetic work.

3. An essentially important feature embodied in the method is a systematic approach to the stereoisomeric problem which complicates sterol synthesis.

4. Several potent estrogenic materials have been prepared. The α- and β-forms of 1,2-dimethyl-7-methoxy-1,2,3,4,9,10-hexahydrophenanthrene-2-carboxylic acid display estrogenic activity when tested by the Kahnt–Doisy method in the order of *0.240* γ and *5.1* γ, respectively.

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