[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. II. Synthesis of *trans*-1,6-Bis-(*m*-hydroxyphenyl)-3-hexene and Related Compounds[1,2]

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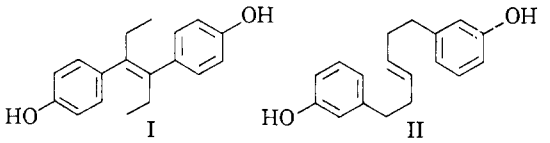
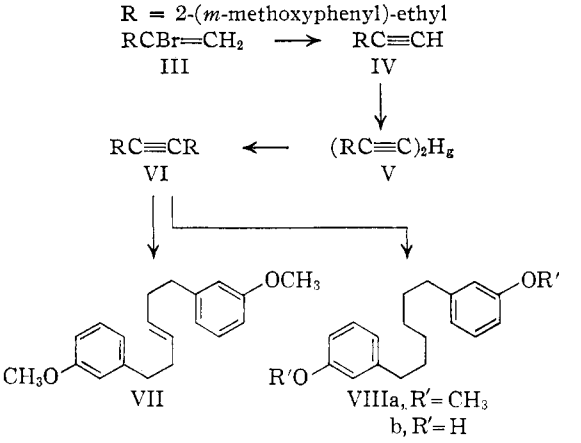
The preparation of some 1,6-diaryl substituted hexenes and hexanes having structural features similar to known biologically active artificial estrogens is described. *trans*-1,6-Bis-(*m*-hydroxyphenyl)-3-hexene (II) was obtained from 1,6-bis-(*m*-methoxyphenyl)-3-hexyne by reduction with sodium in liquid ammonia with subsequent ether cleavage with methylmagnesium iodide at an elevated temperature. 1,6-Bis-(*m*-hydroxyphenyl)-hexane (VIIIb) was obtained by catalytic reduction of 1,6-bis-(*m*-methoxyphenyl)-3-hexyne and demethylation with hydrobromic acid or by treatment of *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexene with sodium and potassium in liquid ammonia. *trans*-1,6-Bis-(*m*-methoxyphenyl)-3-hexen-2-ol (X) was prepared by reduction of the corresponding acetylenic carbinol with lithium aluminum hydride.

Since Cook, Dodds and Hewett first predicted,[4] in 1933, that a group of artificial estrogens would be discovered, well over a thousand compounds with some estrogenic activity have been found.[5,6] The most useful and widely investigated classes of artificial estrogens are the 3,4-diaryl substituted hexenes, hexanes and hexadienes, the best known examples of these classes being diethylstilbestrol (I) hexestrol and dienestrol, respectively.[5] This paper describes the preparation of *trans*-1,6-bis-(*m*-hydroxyphenyl)-3-hexene (II) and related compounds which have structural features similar to the artificial estrogens mentioned above.



An important objective in our work was the preparation of 1,6-bis-(*m*-methoxyphenyl)-3-hexyne (VI), since this compound could be transformed through well established reactions to the corresponding *trans*-olefinic and saturated compounds. An initial attempt to prepare VI by the alkylation of sodium acetylide in liquid ammonia containing sodium amide with 2-*m*-methoxyphenylethyl bromide was unsuccessful. Under the conditions of the reaction the only substance isolated was *m*-methoxystyrene (77% yield).

A stepwise approach to the preparation of the disubstituted acetylene VI, utilizing the methods of Johnson and McEwen[7] and Elsner and Paul[8] was successful. Treatment of *m*-methoxyphenylmagnesium bromide with 2,3-dibromo-1-propene gave 74% of 2-bromo-4-(*m*-methoxyphenyl)-1-butene (III). Dehydrohalogenation of this material with sodium amide in hot Nujol afforded 4-(*m*-methoxyphenyl)-1-butyne (IV) in 79% yield. Conversion of the substituted acetylene to bis-[4-(*m*-methoxyphenyl)-1-butynyl]-mercury (V) was accomplished in 96% yield using alkaline mercuric iodide. The required alkylating agent, 2-*m*-methoxyphenylethyl *p*-toluenesulfonate, was prepared from 2-*m*-methoxyphenylethanol[9] by a published method.[10] Treatment of the mercury derivative V with lithium foil gave the lithium acetylide corresponding to IV which was alkylated[8] with 2-*m*-methoxyphenylethyl *p*-toluenesulfonate to give 1,6-bis-(*m*-methoxyphenyl)-3-hexyne (VI) in 60% yield. Conversion of VI to *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexene (VII) was accomplished in 75% yield by stereospecific reduction[11,12] of the acetylenic bond using sodium in liquid ammonia.



Attempted demethylation of *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexene (VII) by fusing it with pyridine hydrochloride[13] resulted in incomplete ether cleavage and partial isomerization of the *trans*-olefinic bond. Treatment of VII for various periods of time with a mixture of sodium and potassium in liquid ammonia[14] at −33° resulted in only

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(2) Abstracted from the thesis submitted by John C. Wollensak to the Massachusetts Institute of Technology, 1958, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(3) Public Health Service Research Fellow of the National Cancer Institute, 1955–1958.

(4) J. W. Cook, E. C. Dodds and C. L. Hewett, *Nature*, **131**, 56 (1933).

(5) J. Grundy, *Chem. Revs.*, **57**, 281 (1957).

(6) U. V. Solmssen, *ibid.*, **37**, 481 (1945).

(7) J. R. Johnson and W. L. McEwen, THIS JOURNAL, **48**, 469 (1926).

(8) B. B. Elsner and P. F. M. Paul, *J. Chem. Soc.*, 893 (1951).

(9) Prepared from *m*-methoxyphenylacetonitrile [R. B. Woodward, THIS JOURNAL, **62**, 1478 (1940)] by hydrolysis to *m*-methoxyphenylacetic acid [E. R. Shepard, H. D. Porter, J. F. Noth and C. K. Simmans, *J. Org. Chem.*, **17**, 571 (1952)] and reduction with lithium aluminum hydride [by the method of R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2548 (1947)]; also by conversion of *m*-iodoanisole [R. C. Doban, Ph.D. Thesis, University of Wisconsin, 1952] to the Grignard reagent and addition of ethylene oxide [W. E. Bachmann and D. G. Thomas, THIS JOURNAL, **64**, 94 (1942)].

(10) W. F. Johns, R. M. Lukes and L. H. Sarett, *ibid.*, **76**, 5026 (1954).

(11) G. W. Watt, *Chem. Revs.*, **46**, 326 (1950).

(12) R. A. Raphael, "Acetylenic Compounds in Organic Synthesis," Academic Press, Inc., New York, N. Y., 1955, p. 201.

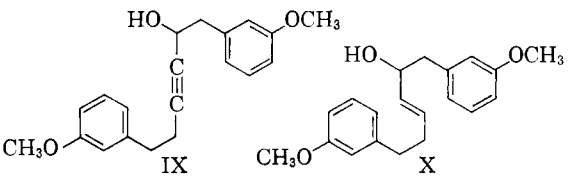
(13) A. L. Wilds and W. B. McCormack, THIS JOURNAL, **70**, 4127 (1948).

(14) K. Freudenberg, W. Lautsch and G. Piazolo, *Ber.*, **74B**, 1879 (1941).

partial demethylation as indicated by infrared and methoxyl determinations of the products. Under more strenuous conditions (room temperature for 25 hours) sodium and potassium in liquid ammonia caused not only quantitative demethylation, but also reduction of the olefinic bond giving 1,6-bis-(*m*-hydroxyphenyl)-hexane (VIIIb) in 98% yield. Amide ion generated in the reaction probably caused migration of the double bond into conjugation with an aromatic ring whereupon it was reduced with the metal–ammonia solution.[15] The same phenol (VIIIb) was obtained by catalytic reduction of 1,6-bis-(*m*-methoxyphenyl)-3-hexyne (VI) using a palladium-on-carbon catalyst, followed by ether cleavage of the intermediate 1,6-bis-(*m*-methoxyphenyl)-hexane (VIIIa) with hydrobromic acid in acetic acid.[13,16]

The demethylation of VII was accomplished finally using methylmagnesium iodide at 175°.[13] Under these conditions, crystalline *trans*-1,6-bis-(*m*-hydroxyphenyl)-3-hexene (II) was obtained in 67% yield. The infrared and ultraviolet spectra of this material are fully consistent with the structural assignment, but do not preclude the possibility of the product being the alternative unconjugated *trans*-1,6-bis-(*m*-hydroxyphenyl)-2-hexene. In order to establish definitely the position of the olefinic double bond, the product was remethylated with dimethyl sulfate to *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexene which has an infrared spectrum that is essentially identical with the spectrum of the previously prepared VII. Cleavage[17] of this material with osmium tetroxide and periodic acid followed by oxidation[18] of the resulting aldehyde with silver oxide gave β-(*m*-methoxyphenyl)-propionic acid which was identical with an authentic sample.[19] The isolation of a propionic acid derivative confirms the location of the double bonds in compounds II and VII.

Another objective of our work was the preparation of *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexen-2-ol (X). Reduction[20] of *m*-methoxyphenylacetonitrile in the presence of semicarbazide using a W-2 Raney nickel catalyst yielded 36% of *m*-methoxyphenylacetaldehyde semicarbazone. Treatment of the semicarbazone with warm 40% aqueous formaldehyde afforded a 64% yield of *m*-methoxyphenylacetaldehyde. Addition of the aldehyde to the Grignard reagent derived from 4-(*m*-methoxyphenyl)-1-butyne (IV) gave 1,6-bis-(*m*-methoxyphenyl)-3-hexyn-2-ol (IX) in 58% yield. The triple bond of IX was reduced stereospecifically[21,22] with lithium aluminum hydride to give 58% of *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexen-2-ol (X).



Model studies of some of the critical condensation reactions in our work led to the preparation of 1-phenyl-3-octyne and 1-phenyl-3-octyn-2-ol. Conversion[7] of di-1-hexynylmercury[23] to 1-hexynyllithium with lithium foil and addition of 2-phenylethyl *p*-toluenesulfonate[24] gave 58% of 1-phenyl-3-octyne. The addition of phenylacetaldehyde to the Grignard reagent derived from 1-hexyne afforded 1-phenyl-3-octyn-2-ol in 40% yield.

Seven of the compounds (II, VI–X) prepared were submitted for biological evaluations. None of the compounds possessed any estrogenic, androgenic or lipodiatic activity.[25] It was felt that the structural similarity of the compounds with known active estrogens should lead at least to estrogenic activity. For example, with molecular models it is possible to coil the substituted hexene chain of II so that the phenolic functions have a comparable spacial arrangement as in diethylstilbestrol (I).[5] This coiled conformation is probably unimportant in solutions; however, in the presence of a chemoreceptor (possibly the enzyme system associated with the chemistry of I) it should be possible to achieve a proper conformation in order for enzymatic reactions to occur.[26] The fact that the compounds are inactive suggests that the chemical reactions leading to an estrus-exciting response may involve not only the phenolic portions of the molecule, but also the aliphatic chain which links the aromatic rings. From a recent review[5] of artificial estrogens, it is apparent that most of the highly active substances have 4-hydroxyphenyl functions separated by two carbon atoms, whereas the present compounds have 3-hydroxyphenyl functions separated by six carbon atoms. These structural differences in our compounds may prevent reactions characteristic of estrogens from occurring; however, other factors may be involved such as solubility properties *in vivo* and rapid metabolism or excretion of the compounds from the test animal.

Experimental[27]

4-(*m*-Methoxyphenyl)-1-butyne (IV).—*m*-Methoxybenzylmagnesium bromide was prepared by adding 20 g. of *m*-

(15) Isolated double bonds are usually inert to sodium in liquid ammonia, whereas conjugated olefins are reduced; see ref. 11, p. 324, and A. J. Birch and H. Smith, *Quart. Revs.*, **12**, 17 (1958).

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

(17) R. Pappo, D. S. Allen, Jr., R. U. Lemieux and W. S. Johnson, *ibid.*, **21**, 478 (1956).

(18) E. Campaigne and W. M. LeSuer, THIS JOURNAL, **70**, 1555 (1948).

(19) Prepared from *m*-methoxybenzyl bromide by the method of R. A. Barnes and L. Gordon, *ibid.*, **71**, 2644 (1949).

(20) H. Plieninger and G. Werst, *Ber.*, **88**, 1956 (1955).

(21) K. R. Bharucha and B. C. L. Weedon, *J. Chem. Soc.*, 1584 (1953).

(22) E. B. Bates, E. R. H. Jones and M. C. Whiting, *ibid.*, 1854 (1954).

(23) T. H. Vaughn, THIS JOURNAL, **55**, 3453 (1933).

(24) (a) D. Klamann, *Monatsh.*, **84**, 54 (1953); (b) S. Winstein, C. R. Lindegren, H. Marshall and L. L. Ingraham, THIS JOURNAL, **75**, 147 (1953).

(25) We are indebted to Dr. V. A. Drill and his associates of the Division of Biological Research of G. D. Searle and Co. for the biological evaluations. Cockerels receiving 10 mg. per kilo per day of the compounds showed normal weight gain. Lipodiatic activity refers to the effect on the phospholipids and cholesterol of the blood plasma.

(26) In much the same way that squalene assumes a coiled conformation before the postulated concerted ring closure occurs to give triterpenes and other polycyclic compounds.

(27) Melting points and boiling points are uncorrected. The infrared spectra were determined with a Baird recording spectrophotometer (model B) fitted with a sodium chloride prism. In reporting infrared spectra, (s) denotes strong, (m) medium and (w) weak absorption. Ultraviolet spectra were determined with a Cary recording spectrophotometer (model 11 MS). Magnesium sulfate was used as the drying agent in this work. The microanalyses were performed by Dr. S. M. Nagy and his associates.

methoxybenzyl bromide[28] in 100 ml. of ether to 15 g. of magnesium turnings in 50 ml. of ether with stirring over a period of 6 hours. Thirty minutes after the addition, the solution of Grignard reagent was run into a solution of 16 g. of 2,3-dibromo-1-propene and 50 ml. of ether with efficient stirring over a period of 2 hours. After the addition was complete, the solution was refluxed for 2 hours, cooled and then poured into 40 ml. of 1 *M* hydrochloric acid and 60 g. of ice. The organic layer was separated, washed with water, dried and concentrated. Distillation of the residue through a short Vigreux column gave 28.65 g. (74%) of **2-bromo-4-(*m*-methoxyphenyl)-1-butene (III)**, b.p. 97–103° (0.32 mm.), $n^{30}D$ 1.5477, $\nu_{max}^{CCl_4}$ 1625(m) and 887(m) cm.$^{-1}$ (terminal methylene). The product was used without further characterization for the preparation of IV.

Sodium amide was prepared by adding 5.28 g. of sodium to about 200 ml. of liquid ammonia containing a few crystals of ferric nitrate. The ammonia was evaporated under a slow stream of nitrogen and 75 ml. of Nujol was added to the sodium amide. The mixture was heated to 150–155° and, with efficient stirring, 22.3 g. of 2-bromo-4-(*m*-methoxyphenyl)-1-butene was added very slowly to prevent excessive foaming. The heating was continued for 2 hours after all of the halide had been added. The mixture was cooled, diluted with 100 ml. of ether, poured onto crushed ice and acidified with cold dilute hydrochloric acid. The organic layer and ether extracts of the aqueous phase were combined, washed with water, dried and concentrated. Fractional distillation of the residue through a short Vigreux column gave 11.7 g. (79%) of the acetylene IV, b.p. 71.5–72° (0.48 mm.), $n^{28}D$ 1.5271.

An analytical sample of this material was obtained from the mercury derivative V described below. A mixture of 100 g. of sodium cyanide, 150 ml. of water and 13 g. of bis-[4-(*m*-methoxyphenyl)-1-butynyl]-mercury was heated on a steam-bath with stirring for 3 hours. The mixture was cooled, extracted with ether and the organic layers were combined and washed with water, dried and concentrated. Distillation of the residue through a short Vigreux column gave 4-(*m*-methoxyphenyl)-1-butyne as a clear colorless liquid, b.p. 83–84° (0.3 mm.), $n^{28}D$ 1.5271, yield 7.15 g. (90%). The analytical sample boiled at 130° (19 mm.).

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.12; H, 7.64.

Bis-[4-(*m*-methoxyphenyl)-1-butynyl]-mercury (V).—To a solution of 81.5 g. of potassium iodide in 81.5 ml. of water was added 33 g. of mercuric chloride followed by 62.5 ml. of 10% sodium hydroxide solution. To this cooled solution was added with mechanical stirring a solution of 18.46 g. of 4-(*m*-methoxyphenyl)-1-butyne in 300 ml. of 95% ethanol. The addition was completed in about 7 minutes and after stirring the mixture for an additional 3 minutes the precipitate was collected on a filter and washed with about 250 ml. of 50% aqueous ethanol. Recrystallization of the precipitate from benzene–petroleum ether produced 28.5 g. (96%) of V as fine white needles, m.p. 86.5–87.5°. The analytical sample melted at 87.8–88.2°.

Anal. Calcd. for $C_{22}H_{22}HgO_2$: C, 50.91; H, 4.26. Found: C, 50.79; H, 4.18.

2-*m*-Methoxyphenylethyl *p*-Toluenesulfonate.—A mixture of 70 ml. of dry pyridine, 13.15 g. of 2-*m*-methoxyphenylethanol (prepared from *m*-hydroxybenzaldehyde or *m*-iodoanisole[9]) and 18.22 g. of *p*-toluenesulfonyl chloride was stirred at 0° for 30 minutes and then allowed to stand overnight in the refrigerator. The product was isolated in the usual way[10] and afforded after recrystallization from benzene–petroleum ether 18.8 g. (71%) of 2-*m*-methoxyphenylethyl *p*-toluenesulfonate, m.p. 37.2–38.3°. The analytical sample melted at 37.5–38.5°.

Anal. Calcd. for $C_{16}H_{18}O_4S$: C, 62.72; H, 5.92. Found: C, 62.73; H, 5.95.

1,6-Bis-(*m*-methoxyphenyl)-3-hexyne (VI).—A mixture of 25.9 g. of bis-[4-(*m*-methoxyphenyl)-1-butynyl]-mercury, 350 ml. of anhydrous, peroxide-free dioxane and 1.4 g. of lithium foil was refluxed under a nitrogen atmosphere for 2 hours. After cooling, the solution of the lithium acetylide was transferred under nitrogen to a clean flask. A solution of 23.3 g. of 2-*m*-methoxyphenylethyl *p*-toluenesulfonate and 250 ml. of anhydrous dioxane was added over a period of 90 minutes with stirring. The mixture was refluxed overnight, cooled, diluted with 500 ml. of water and extracted with ether. The extracts were combined, washed with water, dried and concentrated. Distillation of the residue gave 1.74 g. (22%) of 4-(*m*-methoxyphenyl)-1-butyne and 17.33 g. of 1,6-bis-(*m*-methoxyphenyl)-3-hexyne, b.p. 197–204° (0.13 mm.), which crystallized on standing. Recrystallization from benzene–petroleum ether and from ether gave VI as fine white plates, yield 13.35 g. (60%), m.p. 39–40°. The analytical sample melted at 42.6–43.2°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.57; H, 7.38.

***trans*-1,6-Bis-(*m*-methoxyphenyl)-3-hexene (VII).**—A solution of 14.15 g. of 1,6-bis-(*m*-methoxyphenyl)-3-hexyne and 75 ml. of anhydrous ether was added to 1 l. of liquid ammonia. Ether was added to the liquid ammonia solution until all of the acetylene had dissolved. Then with efficient stirring, 3.34 g. of sodium was added in small portions over a 1-hour period. After stirring the mixture for an additional 1.5 hours, 5 g. of ammonium chloride was added. The ammonia was allowed to evaporate and water and ether were added. The aqueous layer was extracted with ether and the organic layers were combined and washed with dilute sulfuric acid, water, dried and concentrated. Distillation of the residue gave 10.75 g. (75%) of *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexene, b.p. 182.5–184.5° (0.27 mm.), $n^{27}D$ 1.5535, $\nu_{max}^{CCl_4}$ 968(m) cm.$^{-1}$ (*trans*-olefin), λ_{max}^{EtOH} 273 (ϵ 4,040) and 280 mμ (ϵ 3,700).

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.08; H, 8.07.

1,6-Bis-(*m*-methoxyphenyl)-hexane (VIIIa).—A solution of 5 g. of 1,6-bis-(*m*-methoxyphenyl)-3-hexyne and 100 ml. of absolute ethanol was stirred in an atmosphere of hydrogen at atmospheric pressure in the presence of 0.25 g. of an 8% palladium-on-charcoal catalyst. Removal of the catalyst and concentration of the filtrate *in vacuo* gave a yellow oil which on distillation through a short Vigreux column afforded 3.85 g. (76%) of 1,6-bis-(*m*-methoxyphenyl)-hexane, a colorless oil, b.p. 162–164° (0.005 mm.), $n^{29}D$ 1.5574.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.49; H, 8.79. Found: C, 80.17; H, 8.55.

1,6-Bis-(*m*-hydroxyphenyl)-hexane (VIIIb). Method A.[13,16]—A mixture of 2.83 g. of 1,6-bis-(*m*-methoxyphenyl)-hexane, 20 ml. of 48% hydrobromic acid and 115 ml. of glacial acetic acid was refluxed under a nitrogen atmosphere for 18 hours. The reaction mixture was cooled, diluted with ice-water and extracted with ether. The organic layers were combined, washed with 5% sodium bicarbonate solution, water, dried and concentrated *in vacuo*. Two recrystallizations of the solid residue from benzene–hexane gave 2.00 g. (78%) of 1,6-bis-(*m*-hydroxyphenyl)-hexane, m.p. 76–78.4°. Recrystallization of a sample from benzene–hexane followed by sublimation at 190° (0.2 mm.) gave an analytical sample of VIIIb, m.p. 85.2–87.4°.

Anal. Calcd. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.85; H, 8.48.

Method B.[14]—In a 1.5-l. steel bomb with a Pyrex liner, thoroughly dried and flushed with nitrogen, were placed 1.98 g. of 1,6-bis-(*m*-methoxyphenyl)-3-hexene, 150 ml. of liquid ammonia, 2 g. of potassium and 1 g. of sodium. After rocking the mixture at room temperature for 25 hours, the bomb was vented rapidly and isopropyl alcohol was added carefully to discharge the blue color. Ethyl alcohol and then water were added and the alcohols were removed *in vacuo*. The aqueous residue was acidified, extracted with ether and the ether extract was washed with water, dried and concentrated. Crystallization of the residue from benzene–petroleum ether gave 1.75 g. (98%) of 1,6-bis-(*m*-hydroxyphenyl)-hexane, m.p. 81.4–84.4°. The mixed m.p. with VIIIb prepared by method A was 82.4–88.6° and the infrared spectra of the two samples were identical.

***trans*-1,6-Bis-(*m*-hydroxyphenyl)-3-hexene (II).**—To the Grignard reagent from 280 mg. of magnesium and 1.75 ml. of methyl iodide in 15 ml. of dry ether was added 1.16 g. of *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexene. The ether was removed under reduced pressure and the residue was heated at 100° (0.3 mm.) for 30 minutes and at 175° for 90 minutes at atmospheric pressure under nitrogen.[13] Soon after heating the mixture to 175°, a rapid evolution of gas occurred and the mixture swelled up into a solid porous mass. Ether, ethanol and saturated ammonium sulfate solution were

(28) Reference 9, R. B. Woodward.

added successively to the reaction mixture and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried and concentrated. Recrystallization of the residue from benzene gave 0.7 g. (67%) of crude *trans*-1,6-bis-(*m*-hydroxyphenyl)-3-hexene, m.p. 94.4–100.8°. Several recrystallizations of this material from benzene–petroleum ether and benzene, followed by sublimation at 175° (0.25 mm.), gave an analytical sample, m.p. 102.4–105.4°, ν_{max}^{KBr} 3300(s) and 1250(s) cm.$^{-1}$ (phenol) and 973(m) cm.$^{-1}$ (*trans*-olefin), λ_{max}^{EtOH} 274 (ϵ 4,200) and 280 mμ (ϵ 3,800).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.73; H, 7.69.

Proof of Structure of *trans*-1,6-Bis-(*m*-hydroxyphenyl)-3-hexene.—To a mixture of 0.20 g. of *trans*-1,6-bis-(*m*-hydroxyphenyl)-3-hexene, 0.58 g. of potassium hydroxide and 4 ml. of water were added with stirring 4.2 ml. of dimethyl sulfate and a solution of 1.33 g. of potassium hydroxide in 6 ml. of water simultaneously over a 30-minute period. Stirring was continued for 2 hours and then the mixture was extracted with ether. The extracts were washed with water, dried and concentrated giving *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexene (VII) as a light yellow oil. The infrared spectrum of this material is essentially the same as the spectrum of VII prepared by the reduction of the acetylene VI (see above).

The crude ether was dissolved in 5 ml. of benzene and 118 mg. of osmium tetroxide was added. After stirring the mixture at room temperature for 4 hours, 7 ml. of ethanol and then a solution of 0.7 g. of sodium sulfite in 4 ml. of water were added. The mixture was stirred for 30 minutes, filtered through Celite giving a colorless filtrate which was concentrated to a small volume which was diluted with water and extracted with chloroform. The organic layers were combined, washed with water, dried and concentrated *in vacuo* giving 0.20 g. of a yellow oil. This oil was dissolved in a mixture of 4 ml. of methanol and 1 ml. of pyridine and then a solution of 230 mg. of periodic acid in 1 ml. of water was added. The mixture was allowed to stand at room temperature for 1.5 hours before it was diluted with water and extracted with ether. The ether was removed *in vacuo* and the resulting oil was oxidized by adding a mixture of 0.53 g. of silver nitrate and 0.25 g. of sodium hydroxide in 15 ml. of 50% aqueous methanol. The mixture was heated on a steam-bath for 20 minutes and allowed to stand overnight. The solids were filtered from the reaction mixture and the filtrate was extracted with ether. After acidification of the aqueous phase with concentrated hydrochloric acid, it was again extracted with ether and the combined extracts were dried and concentrated *in vacuo* giving 112 mg. of a yellow oil. Crystallization of the oil from benzene–petroleum ether gave 9 mg. of β-(*m*-methoxyphenyl)-propionic acid, m.p. 38–40°, which on recrystallization melted at 42–44° [lit.[29,30] 50–51°]. A mixed m.p. with an authentic sample[19] (m.p. 45–47°) was undepressed (m.p. 42–44°).

***m*-Methoxyphenylacetaldehyde.**—A mixture of 20 g. of *m*-methoxyphenylacetonitrile,[9] 11.2 g. of sodium acetate and 15.3 g. of semicarbazide hydrochloride in 135 ml. of 50% aqueous ethanol was hydrogenated in the presence of about 7 g. of W-2 Raney nickel at an initial pressure of 21 p.s.i. The hydrogenation was completed in 30 minutes at room temperature. Filtration of the catalyst, concentration of the filtrate and cooling gave a precipitate which on recrystallization yielded 8.08 g. (28%) of ***m*-methoxyphenylacetaldehyde semicarbazone** as white needles, m.p. 131.5–132.7°, and 2.07 g. (8%) of a second crop, m.p. 128.5–130°.

Anal. Calcd. for $C_{10}H_{13}N_3O_2$: C, 57.97; H, 6.32. Found: C, 57.68; H, 6.15.

A mixture of 8.82 g. of the semicarbazone and 100 ml. of 40% aqueous formaldehyde was warmed on the steam-bath until a homogeneous solution was obtained and then the solution was cooled and extracted with ether. The organic layers were combined, washed with water, dried and concentrated. Distillation of the residue through a short Vigreux column gave 4.08 g. (64%) of *m*-methoxyphenylacetaldehyde, b.p. 96–98° (0.85 mm.), $\nu_{max}^{CCl_4}$ 2720(w) and 1732(s) cm.$^{-1}$ (aldehyde grouping).

1,6-Bis-(*m*-methoxyphenyl)-3-hexyn-2-ol (IX).—To the Grignard reagent prepared from 0.965 g. of magnesium, 40 ml. of dry ether and 5.41 g. of ethyl bromide was added dropwise 7.96 g. of 4-(*m*-methoxyphenyl)-1-butyne in 25 ml. of ether. The mixture was refluxed for 3 hours, cooled and a solution of 4 g. of *m*-methoxyphenylacetaldehyde and 25 ml. of ether was added over a period of 1.5 hours. The reaction mixture was allowed to stand overnight and was then poured into a cold solution of 10 g. of ammonium chloride and 50 ml. of water and extracted with ether. The ether extract was washed with water, dried and concentrated. A portion (3.32 g.) of the residue was chromatographed on Merck reagent alumina. Elution with 50% benzene in hexane gave 1.0 g. of unchanged 4-(*m*-methoxyphenyl)-1-butyne. Further elution with 1% methanol in ether gave 1.92 g. of 1,6-bis-(*m*-methoxyphenyl)-3-hexyn-2-ol. The remainder of the residue was purified directly by distillation. A total of 2.48 g. of 4-(*m*-methoxyphenyl)-1-butyne was obtained, b.p. 74.2–75° (0.5 mm.), and 4.86 g. (58%) of 1,6-bis-(*m*-methoxyphenyl)-3-hexyn-2-ol (IX), b.p. 215–225° (0.4 mm.). The analytical sample of IX boiled at 215–220° (0.30 mm.), $n^{27}D$ 1.5696, $\nu_{max}^{CCl_4}$ 3600(w) and 3450 (w) cm.$^{-1}$ (hydroxyl) and 2180(w) cm.$^{-1}$ (acetylene).

Anal. Calcd. for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.65; H, 6.80.

***trans*-1,6-Bis-(*m*-methoxyphenyl)-3-hexen-2-ol (X).**—A solution of 4.76 g. of 1,6-bis-(*m*-methoxyphenyl)-3-hexyn-2-ol in 150 ml. of dry ether was added with stirring to a solution of 1 g. of lithium aluminum hydride in 150 ml. of ether over a period of 30 minutes, after which the reaction mixture was refluxed with stirring for 15 hours. The reaction mixture was cooled in an ice-bath and the excess reducing agent was destroyed by adding successively ethyl acetate and saturated ammonium chloride solution. The mixture was extracted with ether and the organic layers were combined and washed with water, dried and concentrated *in vacuo*. Distillation of the residue through a short Vigreux column gave 2.75 g. (58%) of *trans*-1,6-bis-(*m*-methoxyphenyl)-3-hexen-2-ol, b.p. 132–133° (0.001 mm.), $n^{27}D$ 1.5646. The analytical sample had b.p. 210–212° (0.15 mm.), $\nu_{max}^{CCl_4}$ 3600(w) and 3450(w) cm.$^{-1}$ (hydroxyl) and 973(m) cm.$^{-1}$ (*trans*-olefin).

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.89; H, 7.44.

Reaction of 2-*m*-Methoxyphenylethyl Bromide with a Mixture of Sodium Acetylide and Sodium Amide.—A suspension of sodium amide prepared from 2.2 g. of sodium, 50 ml. of liquid ammonia and a crystal of ferric nitrate was added to a solution of sodium acetylide prepared in the usual way[31] from 1.76 g. of sodium, 100 ml. of liquid ammonia and acetylene. 2-*m*-Methoxyphenylethyl bromide (27.4 g.) was added dropwise with vigorous stirring over a 2-hour period. The mixture was stirred for 3 hours after which 70 ml. of water was added slowly. After the ammonia had evaporated, the mixture was extracted with ether and the ether extract was washed with water, dilute hydrochloric acid, water, dried and concentrated. Distillation of the residue gave 13.4 g. (77%) of *m*-methoxystyrene, b.p. 31° (0.12 mm.), $n^{25}D$ 1.5518 [lit.[32,33] b.p. 89–90° (14 mm.), $n^{20}D$ 1.5540]. Treatment of the product with bromine in carbon tetrachloride gave *m*-methoxystyrene bromide, m.p. 66.5–67° (lit.[33] m.p. 66–67°).

1-Phenyl-3-octyne.—To a solution of 12.73 g. of di-1-hexynylmercury[23] in 300 ml. of refluxing, anhydrous dioxane was added 0.983 g. of lithium foil under a nitrogen atmosphere. The exchange reaction required 2 hours. The solution of lithium acetylide was transferred into a dry flask, cooled to room temperature and with efficient stirring, 19.43 g. of 2-phenylethyl *p*-toluenesulfonate[24] in 200 ml. of anhydrous dioxane was added over a period of 1.5 hours under a nitrogen atmosphere. The mixture was then refluxed for 16 hours before adding water and extracting the mixture with ether. The organic layers were combined, washed with water, dried and concentrated *in vacuo*. Distillation of the residue through a short Vigreux column gave 6.92 g. (58%) of 1-phenyl-3-octyne, b.p. 125–130° (0.83 mm.). The analytical sample, distilled through a semimicro column, had b.p. 80° (0.27 mm.), $n^{25}D$ 1.5070.

(29) F. Tiemann and R. Ludwig, *Ber.*, **15**, 2052 (1882).

(30) L. Helfer, *Helv. Chim. Acta*, **7**, 947 (1924).

(31) T. L. Jacobs, "Organic Reactions," Vol. 5, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 26.

(32) A. Klages, *Ber.*, **36**, 3592 (1903).

(33) R. L. Frank, C. E. Adams, R. E. Allen, R. Gander and P. V. Smith, THIS JOURNAL, **68**, 1365 (1946).

Anal. Calcd. for $C_{14}H_{18}$: C, 90.26; H, 9.74. Found: C, 90.18; H, 9.61.

1-Phenyl-3-octyn-2-ol.—A solution of 12 g. of 1-hexyne in 50 ml. of dry ether was added dropwise with stirring to the Grignard reagent prepared from 16.35 g. of ethyl bromide, 3 g. of magnesium turnings and 50 ml. of ether. The reaction mixture was then refluxed for 3 hours, cooled and 8.00 g. of phenylacetaldehyde in 50 ml. of ether was added over 1.5 hours with efficient stirring. The reaction mixture was allowed to stand overnight and then was decomposed by slowly adding it to a solution of 40 g. of ammonium chloride in 150 ml. of water, with external cooling. The layers were separated and the aqueous layer was extracted with ether. The organic layers were combined, washed with water, dried and concentrated *in vacuo*. Distillation of the residue through a short Vigreux column gave 5.37 g. (40%) of 1-phenyl-3-octyn-2-ol, b.p. 116–119° (0.6 mm.). Redistillation of a sample through a semi-micro column gave an analytical sample, b.p. 120–121° (0.77 mm.), $n^{28}D$ 1.5173; $\nu_{max}^{CCl_4}$ 3590(w), 3440(w) and 1030(s) cm.$^{-1}$ (hydroxyl function), and 2180(w) cm.$^{-1}$ (acetylenic bond).

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.14; H, 9.00.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Steroidal Hormone Analogs. III. Reaction of Dimethyl 3,4-*seco*-A-Homocholestanedicarboxylate with Sodium under Acyloin Conditions[1]

BY NORMAN A. NELSON AND ROBERT N. SCHUT[2]

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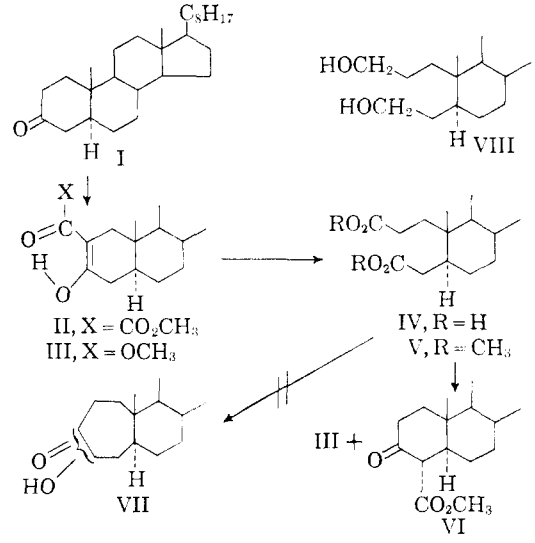
Acylation of cholestan-3-one with dimethyl oxalate gave 2-methoxalylcholestan-3-one which on decarbonylation afforded 2-carbomethoxycholestan-3-one. Treatment of this substance with sodium hydroxide gave 3,4-*seco*-A-homocholestanedicarboxylic acid which was converted to the dimethyl ester. The acyloin condensation of dimethyl 3,4-*seco*-A-homocholestanedicarboxylate using sodium in xylene gave 52% of 2- and 20% of 4-carbomethoxycholestan-3-one.

In connection with the recent work of Gardner, Haynes and Brandon[3] on the formation of Dieckmann reaction products under acyloin conditions, we wish to report our results on the attempted synthesis of a seven-membered ring acyloin in the steroid series. The work described in this paper was undertaken to prepare the cyclic acyloin VII. Similar acyloins in the 19-nor steroid family could serve as intermediates in the synthesis of steroidal tropolones.

Treatment of cholestan-3-one (I) with dimethyl oxalate and sodium methoxide gave, after acidification, 2-methoxalylcholestan-3-one (II) in 85% yield. The structure assigned to the oxalyl derivative II and consequently to the β-keto ester III is based upon the fact that 3-keto steroids belonging to the *trans* series (3-ketoallosteroids) give 2-substituted derivatives in reactions involving intermediate enol formation.[4] The absence of normal ketonic absorption (1700–1725 cm.$^{-1}$ region) in the infrared spectrum of II and the presence of strong bands at 1625 and 1575 cm.$^{-1}$ showed that this compound must be completely enolized.

Pyrolysis of the oxalyl derivative II in the presence of powdered soft glass resulted in the smooth elimination of carbon monoxide and the formation of 2-carbomethoxycholestan-3-one (III) in 66% yield. The infrared spectrum of III showed strong bands at 1660 and 1620 cm.$^{-1}$ characteristic of a chelate structure and also two weak bands at 1740 and 1715 cm.$^{-1}$ indicating[5] that the β-keto ester is not completely enolic. Attempts to prepare III either by direct acylation of cholestan-3-one using dimethyl carbonate and sodium hydride[6] or by acylation of 3-pyrrolidinyl-Δ^2-cholestene[7] using the method of Stork and co-workers[8] were unsuccessful.

Treatment of the β-keto ester III with concentrated sodium hydroxide in refluxing methanol followed by acidification of the reaction mixture gave 92% of 3,4-*seco*-A-homocholestanedicarboxylic acid (IV) which was converted to the dimethyl ester V with diazomethane.



When dimethyl 3,4-*seco*-A-homocholestanedicarboxylate (V) was subjected to the conditions of the

(1) Abstracted from the thesis submitted by Robert N. Schut to the Massachusetts Institute of Technology, 1958, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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(3) P. D. Gardner, G. R. Haynes and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957).

(4) (a) A. Butenandt and A. Wolff, *Ber.*, **68**, 2091 (1935); (b) E. T. Stiller and O. Rosenheim, *J. Chem. Soc.*, 353 (1938); (c) L. Ruzicka, V. Prelog and J. Battegay, *Helv. Chim. Acta*, **31**, 1296 (1948).

(5) (a) N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Peterson, THIS JOURNAL, **74**, 4070 (1952); (b) E. Wenkert and T. E. Stevens, *ibid.*, **78**, 5627 (1956); (c) O. L. Chapman and J. Meinwald, *J. Org. Chem.*, **23**, 162 (1958).

(6) J. Schmidlin, G. Anner, J. R. Billeter, K. Heusler, H. Ueberwasser, P. Wieland and A. Wettstein, *Helv. Chim. Acta*, **40**, 1034 (1957).

(7) F. W. Heyl and M. E. Herr, THIS JOURNAL, **75**, 1918 (1953).

(8) G. Stork, R. Terrell and J. Szmuszkovicz, *ibid.*, **76**, 2029 (1954).