TABLE II

*R*F VALUES OF 2,4-DINITROPHENYLHYDRAZONES

2,4-DNP of	*R*F Value: Cyclohexane-methanol	*R*F Value: Hexane-ether-methanol (20:30:1)
Formaldehyde	0.25	—
Acetaldehyde	0.27	—
Isobutyraldehyde	0.53	—
Acetone	0.45	—
Tiglaldehyde	0.40	—
Levulinaldehyde	0.0	0.0
Succindialdehyde	0.0	0.0
2,4-DNP-reagent	0.0	0.45

TABLE III

YIELDS OF ACETONE FROM CLEAVAGE OF SQUALENE EPOXIDES

Epoxide	Percentage Yield of Acetone on Basis of 2 Moles of Acetone Per Mole of Epoxide
Diepoxyoctahydrosqualene	5.1, 8.5
Tetraepoxytetrahydrosqualene	5.0, 6.5
Hexaepoxysqualene	10.0

and Limborg[19] to give 2,5-dimethoxy-2,5-dihydro-2-methylfuran, b.p. 60–63°/20 mm. (reported[19] b.p. 46–56°/8 mm.). Hydrolysis of this product with dilute sulfuric acid gave 3-acetylacrolein[19] which gave a red crystalline 2,4-dinitrophenylhydrazone, m.p. 270–271° dec. from pyridine-ethanol [reported for 3-acetylacrolein,[27] m.p. 269° dec.]. Ultraviolet in dioxane: λ_{max} 404 mμ, ϵ_{max} 16,000; λ_{max} 450 mμ, ϵ_{max} 15,220. The crude acetylacrolein was hydrogenated with Adams' catalyst in tetrahydrofuran. One mole of hydrogen was absorbed. After filtration and removal of solvent the residue was converted directly to a 2,4-dinitrophenylhydrazone. The yellow needles were recrystallized from pyridine-ethanol, m.p. 233° (reported[28] m.p. 234–235°). Ultraviolet in dioxane: λ_{max} 350 mμ, ϵ_{max} 7530; λ_{max} 420 mμ, ϵ_{max} 4530.

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.38; H, 3.51; N, 24.36. Found: C, 44.73; H, 3.64; N, 24.28.

Spectra. Infrared absorption spectra were measured with a Baird double-beam instrument with sodium chloride optics. Spectra were obtained of 5% solutions in chloroform and 5% solutions in carbon disulfide. In addition, spectra of liquids were determined qualitatively as thin films of pure liquids and spectra of solids were obtained from potassium bromide pellets.

Ultraviolet absorption spectra were obtained on a Process and Instruments automatic recording unit with a Beckman DU spectrophotometer.

NMR spectra were recorded and interpreted by Varian Associates, Palo Alto, Calif. Carbon tetrachloride was used as solvent with added tetramethylsilane as internal standard. Both the spectra reported were obtained at 60 M.C.

Acknowledgment. The authors are indebted to Dr. Norton Nelson for his interest and encouragement in this work and to Mr. C. A. Joseph for technical assistance.

NEW YORK 16, N. Y.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, ARMOUR AND CO.]

Preparation of New Derivatives of Synthetic Estrogens *via* the Claisen Rearrangement[1]

EMIL KAISER AND ELLEN GUNTHER

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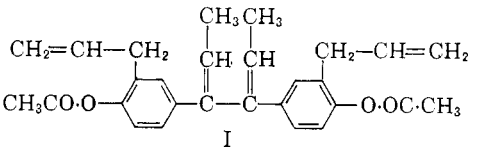
The preparation of 3,3′-diallyldienestrol diacetate from 3,4-bis(4-hydroxyphenyl)-3,4-hexanediol is described. In the course of this synthesis, it was demonstrated that the migratory aptitude of substituents affected the competition between pinacol rearrangement and dehydration in the treatment of a pinacol with acetyl chloride.

The recently reported[2] growth-promoting activity of 3,3′-diallyldiethylstilbestrol and 3,3′-diallylhexestrol[3] in ruminants made it desirable to synthesize other diallyl derivatives of synthetic estrogens. The preparation of 3,3′-diallyldienestrol diacetate (I) was of special interest as its parent compound, dienestrol diacetate, is in use as a poultry growth promotant.



I

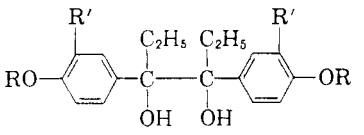
The synthesis of I was originally planned to start with 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) and proceed through the dehydration product of this pinacol, the dienestrol diallyl ether, to the 3,3′-diallyldienestrol and by subsequent acetylation to I.

By analogy with the dehydration of 3,4-bis(4-acetoxyphenyl)-3,4-hexanediol (IIc) to dienestrol diacetate,[4] we expected to obtain the dienestrol

(1) Presented at the 136th meeting of the American Chemical Society, Atlantic City, N. J., Sept. 13–18, 1959.

(2) O. O. Thomas, R. R. Woodward, J. T. Doty, and J. R. Queensberry, *J. Animal Sci.*, **18**, 1498 (1959); I. A. Dyer and A. T. Ralston, *J. Animal Sci.*, **18**, 1499 (1959).

(3) E. Kaiser and J. J. Svarz, *J. Am. Chem. Soc.*, **68**, 636 (1947).

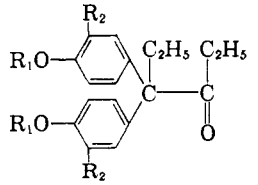


IIa. R = H R′ = H
IIb. R = C_3H_5 R′ = H
IIc. R = CH_3CO R′ = H
IId. R = H R′ = C_3H_5

diallyl ether by refluxing IIb with an acetyl chloride–acetic anhydride mixture. The product of this reaction was an oil which resisted all crystallization attempts. Nevertheless, it was subjected to the Claisen rearrangement in diethylaniline, and crystals with a melting point of 137–138° were isolated. However, this product was not the expected 3,3′-diallyldienestrol, which actually was obtained with a melting point of 123–124° by two other synthetic routes which will be discussed later.

The identity of the substance obtained on refluxing IIb with an acetyl chloride–acetic anhydride mixture was deduced from the infrared absorption spectra of the oily reaction product and its Claisen rearrangement product. In the spectrum of the oil, a peak appeared at 5.86 μ, and shifted to 6.02 μ for the compound which melted at 137–138°. These peaks indicated the presence of a keto group which resulted from a pinacolone rearrangement.[5]

The pinacolone was prepared by a different route to prove that the acetyl chloride–acetic anhydride treatment of IIb really yielded a pinacolone. In this process, the free phenolic pinacol (IIa), was rearranged to 4,4-bis(4-hydroxyphenyl)-3-hexanone (IIIa) with hydrogen chloride in an ether suspension according to Adler, *et al.*[6] With allyl bromide, the diallyl ether of IIIa, an oil, was prepared. This material had an infrared spectrum identical with that of the oil obtained from the acetyl chloride–acetic anhydride reaction mixture, indicating that the two were identical with 4,4-bis(4-allyloxyphenyl)-3-hexanone (III-b). The Claisen rearrangement products (melting point 137–138°) of both oils had identical infrared spectra and melting points. The mixed melting point showed no depression. These identical rearrangement products were 4,4-bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc) instead of 3,3′-diallyldienestrol. The presence of the *p*-allyloxy substituents in the aromatic groups of the pinacol caused pinacolone rearrangement to the corresponding diallyl ether during the acetyl chloride–acetic anhydride reaction. The expected dehydration to dienestrol diallyl ether did not take place.



IIIa. R_1 = H R_2 = H
IIIb. R_1 = C_3H_5 R_2 = H
IIIc. R_1 = H R_2 = C_3H_5

Lane and Spialter[7] used acidic reagents to study the competition between dehydration and pinacol rearrangement in the treatment of IIc and suggested a mechanism for dehydration with acetyl chloride. To Lane and Spialter's findings, we can now add that not only the components of the acidic reagents but also the migratory aptitudes[8] of the groups attached to the pinacol have a bearing upon the competition between pinacolone or diene formation. The rapidly migrating *p*-allyloxyphenyl groups direct the acetyl chloride reaction towards the pinacol rearrangement, and the retarding effect of the *p*-acetoxyphenyl groups permits the formation of the proposed monoacetate intermediate of Lane and Spialter,[7] which in turn dehydrates to a diene.

The hindering effect of the *p*-acetoxyphenyl group on the pinacol rearrangement was further demonstrated when IIc was treated with hydrogen chloride in an ether or methyl ethyl ketone suspension. Contrary to the behavior of IIa,[6] which contains a free phenolic hydroxyl group, the diacetate (IIc) did not undergo a pinacol rearrangement with hydrogen chloride, but was recovered unchanged.

The findings which point out the differences in the behavior of the diallyl ether IIb and the diacetate IIc towards various acidic reagents are summarized in Table I.

TABLE I

PRODUCTS FROM THE TREATMENT OF 3,4-BIS(4-HYDROXYPHENYL)-3,4-HEXANEDIOL (IIa), ITS DIALLYL ETHER (IIb) AND DIACETATE (IIc) WITH ACIDIC REAGENTS

Starting Material	Reagent	Product
Diacetate (IIc)	Acetyl chloride in acetic anhydride or methyl ethyl ketone	Dienestrol diacetate
Diacetate (IIc)	Hydrogen chloride in ether or methyl ethyl ketone	No reaction
Diallyl ether (IIb)	Acetyl chloride in acetic anhydride or methyl ethyl ketone	Pinacolone (IIIb)
Phenol (IIa)	Hydrogen chloride in ether	Pinacolone (IIIa)

According to the evidence presented in Table I, the dehydration of the 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol to 3,3′-diallyldienestrol with acidic

(4) E. C. Dodds, L. Golberg, R. Robinson, and L. Lawson, *Nature*, **142**, 34 (1938); *Proc. Roy. Soc.* (*London*), **B127**, 140 (1939).

(5) J. F. Lane and L. Spialter, *J. Am. Chem. Soc.*, **73**, 4408 (1951).

(6) E. Adler, G. J. Gie, and H. v. Euler, U. S. Patent **2,421,401** (1947).

(7) J. F. Lane and L. Spialter, *J. Am. Chem. Soc.*, **73**, 4411 (1951).

(8) G. H. Wheland, *Advanced Organic Chemistry*, second ed., John Wiley & Sons, Inc., New York, 1949, p. 515.

reagents was prevented by the rapid shifting of a *p*-allyloxyphenyl group from the 3 to the 4 position of the hexanediol. To avoid this pinacol rearrangement, the *p*-ether linkages had to be eliminated. This was accomplished *via* the Claisen rearrangement, which transformed IIb into the oily 3,4-bis(3-allyl-4-hydroxyphenyl)-3,4-hexanediol, IId. This was acetylated and dehydrated in one step by using an acetyl chloride-acetic anhydride mixture. The resulting crystalline product was the desired 3,3′-diallyldienestrol diacetate (I).

For structural confirmation, 3,3′-diallyldienestrol diacetate was also synthesized from dienestrol diallyl ether prepared from dienestrol with allyl bromide. The dienestrol diallyl ether was rearranged to the 3,3′-diallyldienestrol, a crystalline product, *via* the Claisen rearrangement. Subsequent acetylation of the rearranged compound yielded 3,3′-diallyldienestrol diacetate (I), identical in melting point and infrared spectrum with the product obtained from the oily 3,4-bis(3-allyl-4-hydroxyphenyl)-3,4-hexanediol.

The estrogenic activity of 3,3′-diallyldienestrol was found to be in the range of 0.2% of that of diethylstilbestrol. This assay, conducted by Dr. H. D. Lennon of the Research Division of Armour and Company, was done by the immature-mouse uterine weight method of Evans, *et al.*[9] The compound was injected subcutaneously in the test animals and its potency calculated from the standard dose-response curve of diethylstilbestrol according to the general method of Bliss.[10]

EXPERIMENTAL[11]

Meso-3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb). A mixture of *meso*- and *racemic*-3,4-bis(4-hydroxyphenyl)-3,4-hexanediols[12] was acetylated and the *meso*-diacetate separated from the racemic diacetate by crystallization from butanol. Saponification of the *meso*-diacetate yielded pure *meso*-II-a.[13] Twenty-four grams of *meso*-II-a and 26 g. of anhydrous potassium carbonate were stirred with 100 ml. of methyl ethyl ketone and, at reflux temperature, 15.6 ml. of allyl bromide was added dropwise. Refluxing was continued for 13 hr., the solid removed by filtration, and the filtrate evaporated. The residue was crystallized from ethanol and 24.5 g. of *meso*-3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb), m.p. 134–136°, was obtained.

Anal. Calcd. for $C_{24}H_{30}O_4$: C, 75.36; H, 7.90. Found: C, 75.14; H, 7.95.

4,4-Bis(4-allyloxyphenyl)-3-hexanone (IIIb). A 1.9-g. sample of 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) was refluxed with a mixture of 10 ml. of acetyl chloride and 10 ml. of acetic anhydride for 4 hr. The mixture was poured into 300 ml. of water, stirred, and extracted with ether. The organic layer was dried over sodium sulfate and the ether was evaporated. The residue was an oil which could not be crystallized. The infrared absorption spectrum of the oil showed a peak at 5.86 μ, indicating the presence of a keto group.

4,4-Bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc). The oil IIIb, obtained in the previous step, was refluxed for 4 hr. with 20 ml. of diethylaniline in an atmosphere of nitrogen. After it had been cooled, the reaction mixture was poured into 300 ml. of 2*N* hydrochloric acid, stirred vigorously, and then extracted with ether. The dried ether extract was reduced to a small volume. Petroleum ether (b.p. 40–60°) was added to the concentrated ether solution until a precipitate began to form. The precipitate was removed by filtration and discarded. The filtrate was mixed with sufficient petroleum ether (b.p. 40–60°) to produce turbidity. Crystals formed when the mixture was chilled. They were collected and dried. The yield of 4,4-bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc) was 0.6 g., m.p. 137–138°. A ketone peak at 6.02 μ was present in the infrared spectrum of the compound.

Anal. Calcd. for $C_{24}H_{28}O_3$: C, 79.08; H, 7.74. Found: C, 79.15; H, 7.68.

4,4-Bis(4-hydroxyphenyl)-3-hexanone (IIIa). This compound was prepared according to the process of Adler, *et al.*[6] by passing hydrogen chloride through an ether suspension of IIa. An oil (IIIa) was isolated from the ether solution. This oil solidified on standing. Compound IIIa showed a ketone peak at 5.93 μ.

4,4-Bis(4-allyloxyphenyl)-3-hexanone (IIIb) *from* IIIa. Five grams of compound IIIa was treated with allyl bromide in the same manner as described for the preparation of compound IIb from compound IIa.

An oil isolated from the reaction mixture had the same infrared absorption spectrum as the oil IIIb which had been obtained by the acetyl chloride-acetic anhydride treatment of 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol. This identical spectrum proved that the compound was 4,4-bis(4-allyloxyphenyl)-3-hexanone.

4,4-Bis(3-allyl-4-hydroxyphenyl)-3-hexanone (IIIc) *from* IIIb. Five grams of compound IIIb prepared from IIIa was rearranged in diethylaniline as described for the preparation of compound IIIc from the oily product IIIb of the acetyl chloride-acetic anhydride reaction. A 4.3-g. sample of IIIc was obtained. This compound had the same melting point and infrared absorption spectrum as described previously, which identified it as 4,4-bis(3-allyl-4-hydroxyphenyl)-3-hexanone.

Treatment of meso-3,4-bis(4-acetoxyphenyl)-3,4-hexanediol (IIe) *with hydrogen chloride.* One gram of *meso*-3,4-bis(4-acetoxyphenyl)-3,4-hexanediol (IIe) was suspended in 20 ml. of ether, and hydrogen chloride gas was passed through the suspension for 8 hr. The suspension did not clear and the solid was collected from it on a filter. The melting point and infrared spectrum of the solid were identical with those of the starting material. The filtrate was evaporated to dryness. Only traces of an oil remained after the ether had been evaporated. The same treatment was carried out in a methyl ethyl ketone suspension and again unchanged IIe was recovered.

Dehydration of meso-3,4-bis(4-hydroxyphenyl)-3,4-hexanediol (IIe) *with acetyl chloride in methyl ethyl ketone.* Twenty grams of IIe was refluxed with a mixture of 100 ml. of acetyl chloride and 100 ml. of methyl ethyl ketone for 22 hr. All of the solid dissolved. Water and ether were added, and after the acetyl chloride decomposed, the solvent layer was separated from the aqueous layer. The organic layer was dried over sodium sulfate and evaporated to dryness. The residue was crystallized from ethanol and 5.2 g. of dienestrol diacetate, m.p. 120–122°, was obtained.

Dienestrol diacetate was obtained also from the racemic form of IIe with acetyl chloride in the methyl ethyl ketone dehydration process.

(9) J. S. Evans, R. F. Varney, and F. C. Koch, *Endocrinology*, **28**, 747 (1941).

(10) C. I. Bliss, *The Statistics of Bioassay*, Academic Press, Inc., New York, 1952, p. 566, ff.

(11) Microanalyses were performed by Midwest Microlab., Inc., Indianapolis 20, Ind.

(12) Mr. W. E. Irwin from the Miles Chemical Co., Elkhart, Ind., furnished a generous sample of the pinacol mixture.

(13) E. Adler, U. S. Patent **2,465,505** (1949).

3,3-Diallyldienestrol diacetate from IIb. To 15 ml. of diethylaniline, 1.91 g. of 3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) was added and the solution refluxed under nitrogen for 6 hr. The reaction mixture was poured into 200 ml. of 2*N* hydrochloric acid, stirred, and then extracted with ether. The ether extract was washed with water, dried over sodium sulfate, and the solvent evaporated. The residue, a viscous oil, was used without further purification for dehydration to 3,3′-diallyldienestrol diacetate. The dehydration was carried out by refluxing the oil, *meso*-3,4-bis(3-allyl-4-hydroxyphenyl)-3,4-hexanediol, with a mixture of 10 ml. of acetyl chloride and 10 ml. of acetic anhydride for 4 hr. Four hundred milliliters of water was added and the mixture extracted with ether. The ether extract was washed with a sodium bicarbonate solution, then with water, dried over sodium sulfate, and the ether evaporated. The residue was crystallized from ethanol and then recrystallized from an ether–petroleum ether (b.p. 40–60°) mixture. The 3,3′-diallyldienestrol diacetate melted at 145–147° and its yield was 0.25 g.

Anal. Calcd. for $C_{28}H_{30}O_4$: C, 78.11; H, 7.02. Found: C, 78.09; H, 7.18.

3,3′-Diallyldienestrol diacetate from dienestrol. Dienestrol was treated with allyl bromide in the same manner as described for the preparation of compound IIb. Dienestrol diallyl ether was rearranged in diethylaniline to form 3,3′-diallyldienestrol, which was then crystallized from an ether–petroleum ether (b.p. 40–60°) mixture and recrystallized from dilute ethanol. The 3,3′-diallyldienestrol melted at 123–125°.

Anal. Calcd. for $C_{24}H_{26}O_2$: C, 83.21; H, 7.28. Found: C, 83.12; H, 7.35.

The 3,3′-diallyldienestrol quickly discolored upon exposure to air but remained colorless when the hydroxyl groups were acetylated. Acetylation with acetic anhydride or a pyridine–acetic anhydride mixture gave very poor yields but acetylation of the sodium salt of the 3,3′-diallyldienestrol with acetic anhydride produced the diacetate in good yields. Six grams of 3,3′-diallyldienestrol was dissolved in 100 ml. of 30% aqueous ethanol containing 1.9 g. of sodium hydroxide. The solution was evaporated to dryness under reduced pressure and the residue refluxed for 7 hr. with 150 ml. of acetic anhydride. The acetic anhydride was decomposed with water and the remaining solid was collected on a filter and crystallized from ethanol. A 5.1-g. sample of 3,3′-diallyldienestrol diacetate was obtained. The compound was identical in melting point and infrared spectrum with the product obtained from the *meso*-3,4-bis(4-allyloxyphenyl)-3,4-hexanediol (IIb) through Claisen rearrangement, acetylation, and dehydration.

CHICAGO 9, ILL.

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY AND THE DEPARTMENT OF CHEMISTRY, ST. JOSEPHS COLLEGE[1]]

Steroidal Sapogenins. LXIII. Chiapagenin, a New Normal (25 L) Δ^5-12β-Hydroxysapogenin[2]

SAMUEL SEROTA,[3a] ROBERT P. KOOB,[3b] AND MONROE E. WALL[3c]

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A new normal Δ^5-12β-hydroxysapogenin, for which the name chiapagenin is proposed, has been isolated from the tubers of Dioscorea chiapasensis Matuda.[4] Unequivocal proof of structure was obtained by catalytic hydrogenation of chiapagenin followed by acidic isomerization at C_{25} to give the known 5α,12β-hydroxysapogenin rockogenin. Reduction of the known normal Δ^5-12-ketosapogenin correllogenin with lithium in liquid ammonia containing methyl alcohol gave chiapagenin. Therefore the latter must be 12β-hydroxyyamogenin.

During the course of investigations of the plant kingdom for steroidal sapogenins, a new sapogenin was isolated from *Dioscorea chiapasensis* Matuda[4] and identified. The two sapogenins present in this plant were separated by chromatography. The first product eluted was identified as the Δ^5-normal (25 L) sapogenin, yamogenin, by direct comparison with an authentic sample. Further elution gave a more polar, obviously polyhydroxy, sapogenin. The melting points of the latter compound and its acetate did not correspond to any previously known sapogenin. The structure of the new sapogenin, for which the name chiapagenin is proposed, was established in the following manner. Analysis of the new sapogenin and its acetate showed two hydroxyl groups present and the typical C_{27} skeleton found in steroidal sapogenins. The infrared spectrum of chiapagenin diacetate showed this sapogenin to have the normal spiroketal side chain[5,6] with bands characteristic of Δ^5-unsaturation.[7,8] This latter feature of the molecule

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, United States Department of Agriculture, Philadelphia 18, Pennsylvania, and St. Joseph's College, Philadelphia 31, Pennsylvania.

(2) Previous paper in this series, Steroidal Sapogenins. LXII, M. E. Wall and S. Serota, *Tetrahedron*.

(3) (a) Eastern Utilization Research and Development Division, Philadelphia 18, Pennsylvania. Abstracted from a thesis submitted to the Department of Chemistry, St. Joseph's College, Philadelphia 31, Pennsylvania, in partial fulfillment of the requirements for the degree of Master of Science. (b) Professor of Chemistry, St. Joseph's College, Philadelphia 31, Pennsylvania. (c) Eastern Utilization Research and Development Division, Philadelphia 18, Pennsylvania.

(4) Identified by Dr. E. Matuda, Instituto Biologico, University of Mexico, Villa Obregón, Mexico, D. F.

(5) M. E. Wall, C. R. Eddy, M. L. McClennan, and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

(6) R. N. Jones, E. Katzenellenbogen, and K. Dobriner, *J. Am. Chem. Soc.*, **75**, 158 (1953).

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(8) C. R. Eddy, M. E. Wall, and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953).