mother liquors. The analytical sample was recrystallized from acetone-ether, m.p. 203–206°; $[\alpha]_D^{CHCl_3}$ +114°; $\lambda_{max}^{CHCl_3}$ 2.80–2.90, 5.74, 5.79, 5.84, 8.1 μ.

Anal. Calcd. for $C_{25}H_{36}O_6$: C, 69.41; H, 8.39. Found: C, 69.59; H, 8.48.

16,16-Dimethylprednisone 21-acetate (XIV). To a stirred solution of 250 mg. of 21-acetoxy-16,16-dimethylpregnane-17α-ol-3,11,20-trione (XIII) in 5 ml. of chloroform and 0.1 ml. of acetic acid at 0–5° was added 193 mg. of bromine in 5 ml. of chloroform and 1 ml. of acetic acid (time, 25 min.). To the colorless solution was added 120 mg. of sodium acetate in 2 ml. of water, followed by additional water and chloroform. The mixture was extracted with chloroform and the latter extract washed with dilute aqueous potassium bicarbonate and saturated salt solution and dried over magnesium sulfate. The colorless residue (350 mg.) of *2,4-dibromo - 21 - acetoxy - 16,16 - dimethylpregnane - 17α - ol-3,11,20-trione* was dehydrobrominated as follows[14]: It was dissolved in 3 ml. of dimethylformamide, 100 mg. of sodium bromide was added and the mixture stirred at 25° under nitrogen for 1 hr. Dimethylaniline, 0.5 ml., was added and the temperature raised to 135° for 2.5 hr. The purple solution was cooled to 10° and 0.4 ml. of concd. hydrochloric acid in 15 ml. of water was added dropwise. The precipitated crude product was filtered, washed with water, and dried in air. The precipitate was dissolved in ethyl acetate, passed through a column of 1 g. of unground charcoal, which was eluted with ethyl acetate. Crystallization of the residue (225 mg.) of the first 50 ml. eluate from acetone-ether gave 82 mg. of XIV as hexagonal plates, m.p. 224–228°. The analytical sample was recrystallized from acetone-ether, m.p. 231–235°; $[\alpha]_D^{CHCl_3}$ +210°; $\lambda_{max}^{CH_3OH}$ 238 mμ (14,200); $\lambda_{max}^{CHCl_3}$ 2.85, 5.73, 5.76, 5.84, 6.00, 6.14, 6.19 sh., 8.06, 11.20 μ.

Anal. Calcd. for $C_{25}H_{32}O_6$: C, 70.08; H, 7.53. Found: C, 70.02; H, 7.42.

The NMR spectrum of XIV in deuterochloroform was consistent with the normal steroid C-18 methyl (8.90 τ) and side chain structures (21-acetoxymethyl, 5.11 τ) and inconsistent with the isomeric D-homoannulated structures (see ref. 8). Similarly the infrared bands at 5.73 and 5.76 μ are as expected for the normal steroid C-21:C-20-CH_2O-C_2H_3O C=O part structure.

(14) Procedure of J. Day, R. Erickson, and R. Pettebone, U. S. Patent 2,873,284 (1959).

RAHWAY, N. J.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX S. A.]

Steroids. CLXXVI. Claisen Rearrangement of Estrone Allyl Ether[1]

P. G. HOLTON

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Rearrangement of estrone allyl ether in refluxing diethylaniline gave a 3:1 mixture of 4-allyl- (III) and 2-allylestrones (II). Each isomer has been reduced to the corresponding C-allyl and C-propylestradiol. Structural assignments have been made on the basis of NMR, infrared and ultraviolet spectra, and on molecular rotation relationships.

The Claisen rearrangement of estrone allyl ether was first carried out by Miescher and Scholz.[2] Their product was noncrystalline but rearrangement was demonstrated to have occurred by the preparation of a crystalline benzoate. Very recently, Patton[3] has shown that both 2-allyl- and 4-allylestrones could be isolated from the rearrangement in crystalline form and he assigned structures to the two isomers on the basis of characteristic C—H deformation bands in the infrared absorption spectra.

While the structural assignments made by Patton are undoubtedly correct, the evidence provided by these absorption bands is not completely unequivocal in the case of the C-allylestrones themselves.

The results now presented are an independent study in which much physical evidence, based on NMR, infrared, and ultraviolet spectra as well as on molecular rotations, has been assembled not only for the C-allylestrones but for certain reduction products.

Rearrangement of estrone allyl ether, under essentially the original reaction conditions,[2,4] gave a product which was only poorly separated by chromatography on silica. However, slow fractional crystallization from ether-hexane resulted in complete separation of the two isomers. The less soluble isomer, to which the 2-allyl structure was assigned, crystallized in colorless plates, m.p. 186–187°, and the more soluble 4-allylestrone separated as rosettes of broad, flat needles, m.p. 136–137°. The ratio of isomers was 1:3 with the latter predominating.

Each isomer was characterized as a crystalline benzoate and a mixture of these in the correct proportions melted at the same temperature as that reported for the benzoate of Miescher and Scholz.[2] Reduction of the C-allylestrones, II and III, by sodium borohydride in aqueous methanol gave the corresponding C-allylestradiols, IV and V, and these were hydrogenated over Adams' catalyst in ethanol to the C-propylestradiols VI and VII.

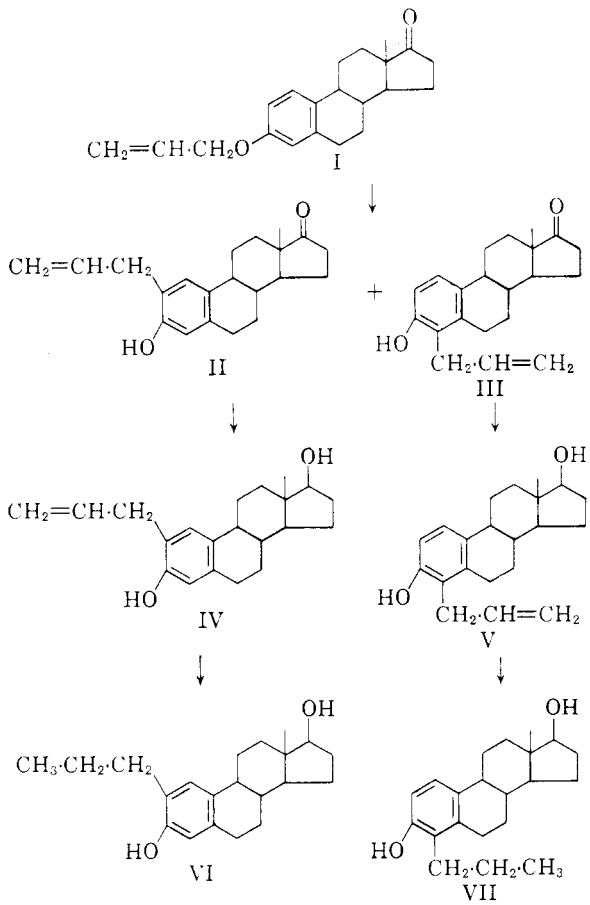
The distribution of isomers formed in the rearrangement is, at first sight, unusual and would not

(1) Steroids. CLXXV., P. G. Holton and E. Necochea, *J. Pharm. Med. Chem., in press.*

(2) K. Miescher and C. Scholz, *Helv. Chim. Acta*, 20, 1237 (1937).

(3) T. L. Patton, *Chem. & Ind.* (London), 1567 (1960).

(4) The lower boiling point of diethylaniline (176°/570 mm.) necessitated extension of the reaction time to 10 hr. After 5 hr., the original reaction period of Miescher and Scholz,[2] 20% of the ether remained unrearranged.



have been predicted by analogy with simpler systems, since the allyl ethers of 3,4-disubstituted phenols usually rearrange to the symmetrically tetrasubstituted product. The relative proportions of the isomers is reminiscent of those resulting from the nitration of estrone and estradiol, when the 4-nitro isomer is obtained to at least as great an extent as the 2-isomer.[5]

According to the accepted mechanistic interpretation of the Claisen rearrangement as proceeding by an intramolecular nucleophilic substitution, the allyl group becomes attached to the *ortho*-position of higher electron density and thus in 3,4-disubstituted compounds a parallelism in product distribution between the Claisen rearrangement and electrophilic substitution in the corresponding phenol is to be expected. In practice this is invariably found to be the case, for the 2′-methylallyl ether of the 3,4-xylenol rearranges to 6-(2′-methylallyl)-3,4-dimethylxylenol,[6] while nitration of 3,4-dimethylxylenol gives a large preponderance of the 6-nitro isomer.[7] Similarly the rearrangement of 2-allyloxy-5,6,7,8-tetralin gives 3-allyl-2-hydroxytetralin[8] while nitration of 2-hydroxy-5,6,7,8-tetralin gives exclusively the 3-nitro isomer.[9]

In these reactions the contrasting behavior between estrone and estradiol and the corresponding tetralin derivative is particularly striking. That the 4- position in the tetracyclic series becomes the position of greater electron density must be due to the fusion of a rigid tricyclic structure to the aromatic ring.

Turning to the identities of the rearrangement products, the proton magnetic resonance spectra of the two *o*-allylphenols, II and III, and of their tetrahydro derivatives, VI and VII, permitted definite assignments of structures.[10]

One of the allylestrones, m.p. 136–137°, and the corresponding *n*-propylestradiol displayed benzene ring two-proton absorption characteristic of an AB system with spin-spin coupling giving rise to two asymmetric doublets.[11] The coupling constant, J_{AB}, equal to 8.5 c/s, is as expected for the coupling of two *ortho* hydrogens. Only structures III and VII are compatible with this absorption pattern. The remaining two compounds displayed benzene ring proton absorption as two singlets each equivalent to one hydrogen atom as required by structures II and VI.

The asymmetry of the doublets for the AB system in III and VII is in accord with the ratios $J_{AB}/\delta_B-\delta_A = 0.40$ and 0.32, respectively.[12]

Table I lists the principal absorption bands,

(5) A. J. Tomson and J. P. Horwitz, [*J. Org. Chem.*, **24**, 2056 (1959)] obtained 38% of the 2-nitro and 44% of the 4-nitro isomer in the nitration of estrone, and T. L. Patton [*J. Org. Chem.*, **24**, 1795 (1959)] obtained 29% of the 2-nitro and 28% of the 4-nitro isomer in the nitration of estradiol.

(6) Q. R. Bartz, R. F. Miller, and R. Adams, *J. Am. Chem. Soc.*, **57**, 371 (1935).

(7) A. C. Holler, C. Huggett, and F. H. Rathmann, *J. Am. Chem. Soc.*, **72**, 2034 (1950).

(8) S. I. Sergievskaya and A. E. Garrilova *J. Gen. Chem. (U.S.S.R.)*, **11**, 1027 (1941); *Chem. Abstr.*, **39**, 4601 (1941).

(9) H. Thoms and W. Kross, *Arch. Pharm.*, **265**, 336 (1927).

(10) NMR spectra were determined on a Varian Associates HR 60 spectometer using a 60-mc. oscillator and deuterochloroform solutions of undeuterated steroids. An integrator was used for intensity measurements and calibration was by the standard sideband technique. Thanks are due to Mr. Paul Landis of Eli Lilly and Co. for carrying out these determinations and confirming the position of the allyl group. The author especially thanks Dr. A. D. Cross for the interpretations given in Table I.

(11) L. M. Jackman *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, Pergamon Press, London, 1959, pp. 89 and 90.

(12) The chemical shift, $\delta_B-\delta_A$, between these doublets has been calculated from the equation $(1-3) = (2-4) = \sqrt{(\delta_B - \delta_A)^2 + J_{AB}^2}$ where the numbers 1 to 4 refer to the positions of the four bands in order of increasing shielding and the quoted values for these doublets (Table I) are arrived at by the addition and substraction of $\frac{\delta_B - \delta_A}{2}$ to the midpoint X of the doublets.[11] For definition of τ, see G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

The coupling *para* hydrogens on the benzene ring is known to occur giving doublets with $J < 1$ c/s. This fine splitting was not observed in the spectra of II and VI.

TABLE I

NMR SPECTRA OF SUBSTITUTED ESTRONES AND ESTRADIOLS PROTON ASSIGNMENTS AND τ VALUES

Protons	Splitting	No. of H's	4-Allylestrone (III)	4-*n*-Propylestradiol (VII)	2-Allylestrone (II)	2-*n*-Propylestradiol (VI)
C-18 methyl	Singlet	3	9.10 (3)	9.27 (3)	9.13 (3)	9.21 (3)
Methyl of *n*-propyl	Triplet	3	—	8.93, 9.03, 9.14 (3)	—	8.93, 9.03, 9.14 (3)
C-6 and C-9 benzylic hydrogens	Unresolved multiplet	3	7.18 (3)	Broad absorption around 7.40 (5)	7.24 (3)	Broad absorption around 7.59 (5)
Side chain benzylic hydrogens	Doublet for allyl compounds	2	6.49, 6.60 (2)		6.61, 6.73 (2)	
Terminal methylene	See ref. 13	2	4.85, 5.10 (2)	—	4.83, 5.06 (2)	
Vinylic =CH—	Multiplet	1	4.03 (1)	—	4.19 (1)	—
C-1 and C-2 phenyl hydrogens	Two doublets	2	2.91, 3.25 (2)	2.95, 3.38 (2)	—	—
C-1 and C-4 phenyl hydrogens	Two singlets	2	—	—	2.97, 3.44 (2)	2.96, 3.50 (2)

Figures in parentheses after τ values are observed relative absorption areas.

relative intensities and proton assignments for the phenols II, III, VI, and VII.[13]

Patton[3] made use of the C—H out-of-plane deformation vibrational bands in the 800–900 cm.$^{-1}$ region of the infrared absorption spectra to differentiate between the two C-allylestrones. 4-Allylestrone, with two adjacent ring hydrogens, would be expected to display an absorption band in the 860–800-cm.$^{-1}$ region while 2-allylestrone, with only isolated ring hydrogens, would show a band at lower wave lengths in the 900–860-cm.$^{-1}$ range.[14]

In fact, in the case of 2-allylestrone the principal band in this region falls at 877 cm.$^{-1}$, but there are additional twin peaks at 830 and 822 cm.$^{-1}$ For 4-allylestrone, the principal absorption band is at 814 cm.$^{-1}$, with a shoulder at 820 cm.$^{-1}$ but additional smaller bands occur at 882 and 865 cm.$^{-1}$

These complications are not present to the same extent in the corresponding estradiols. As shown in Table II the bands for the 2-substituted compounds occurs at 872–880 cm.$^{-1}$ and for the 4-substituted compounds at 811–812 cm.$^{-1}$ and, at least in the case of the propylestradiols, there is no other significant absorption in this region.

The C=C stretching modes in benzenoid compounds give rise to a group of four bands between 1650 and 1450 cm.$^{-1}$ of which those close to 1600 cm.$^{-1}$ and 1500 cm.$^{-1}$ are the most clearly defined and have been used for the diagnosis of substitution patterns since their position is influenced largely by the arrangement of substituents and is to a great extent independent of their nature.[15]

For 1,4-disubstituted and 1,2,4-trisubstituted compounds both the 1600 cm.$^{-1}$ and 1500 cm.$^{-1}$ bands are shifted to slightly higher frequencies while in vicinal trisubstituted compounds they occur at slightly lower frequencies, as would be expected from a consideration of simple oscillator models. By extension of this concept to tetrasubstituted compounds, the 2-substituted estrogens with a 1,2,4,5-substitution pattern, will be those displaying band frequencies higher than in the corresponding 4-substituted estrogens with a 1,2,3,-4-substitution pattern. As shown in Table II, the assigned structures are in agreement with this generalization and a reasonably constant increment of 20–25 cm.$^{-1}$ is found for both the 1600 and 1500 cm.$^{-1}$ bands.

The benzenoid band of variable intensity which often occurs near 1580 cm.$^{-1}$ is apparent in the 2-

(13) The NMR spectra provide considerable evidence for intramolecular hydrogen bonding in the *o*-allylphenols. A more detailed discussion of this aspect and a correlation of the chemical shifts and splittings of several proton absorptions in these spectra will be presented separately by Dr. A. D. Cross.

(14) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd. ed., Methuen, London, 1958, pp. 78–79. See also, H. Dannenberg, U. Schiedt and W. Stiedle. *Z. Naturforsch*, **8b**, 269 (1953); I. Scheer, W. R. Nes, and P. B. Smelzer, *J. Amer. Chem. Soc.*, **77**, 3300 (1955).

(15) See ref. 14, pp. 69–73.

TABLE II

AROMATIC C=C STRETCHING VIBRATIONS AND AROMATIC C—H DEFORMATION VIBRATIONS IN I.R. ABSORPTION SPECTRA

Compound	C=C Stretching Vibrations			C—H Out-of-Plane Deformation Vibrations	
	1600-cm.$^{-1}$ band	1580-cm.$^{-1}$ band	1500-cm.$^{-1}$ band	2-Adj. ring H	Isolated ring H
2-Allylestrone	1618	1592	1511	—	877
2-Allylestradiol	1619	1586	1503	—	880
2-Propylestradiol	1618	1591	1512	—	872
4-Allylestrone	1593	not detectable	1492	814	—
4-Allylestradiol	1594		1479	812	—
4-Propylestradiol	1593		1490	811	—

substituted compounds in the range 1586–1592 cm.$^{-1}$, being well defined in the case of 2-allylestrone and weaker in the estradiols, but is not discernible in the 4-substituted compounds.

Information regarding the pattern of substitution in benzenoid derivatives can often be obtained from ultraviolet absorption since the bathochromic shifts and, more particularly, the intensity changes brought about by introduction of an auxochrome are dependent on its position. For substituents which interact only weakly with the aromatic ring, the introduction of a third substituent *para* to an existing group in a disubstituted compound, causes an increase in intensity as a consequence of greater charge separation in the excited state while substitution *ortho* to an existing group causes a reduction in intensity.[16] For alkyl substituents the effect is well exemplified by the intensities of the B-bands of 1,2,4-trimethylbenzene (ϵ = 835) and 1,2,3-trimethylbenzene (ϵ = 360) as compared with *o*-xylene (ϵ = 415).[17] On this basis, the 2-substituted estrogens should display increased intensities as compared with estrone and the 4-substituted estrogens should display reduced intensities. The data given in Table III show this to be the case. A similar increase in intensity is shown by 2-methylestrone and 2-methylestradiol prepared by Iriarte and Ringold,[18] and a reduction in intensity is exhibited by 4-methylestradiol.[19] The bathochromic shifts produced by introduction of alkyl substituents into the aromatic chromophore are of the expected magnitudes, being greater for the 2-substituents.

Finally, since closely related substituents in the same position should exert comparable effects on the molecular rotation, agreement is to be expected between compounds assigned the 2-substituted structures and the 2-methylestrogens of Iriarte and Ringold.[18] In Table III it is seen that the molecular rotations are indeed similar, agreement being particularly good for the 2-methyl- and 2-propylestradiols where the substituents are more closely related.

TABLE III

OPTICAL DATA FOR SUBSTITUTED ESTRONES AND ESTRADIOLS

Compound	$[\alpha]_D$ Dioxane	$[M]_D$	C_2H_5OH λ_{max} mμ	ϵ
Estrone	+163°	+460	280	2340
2-Methylestrone	+198°	+586	283	2570
2-Allylestrone	+152.2°	+473	284–6	3020
4-Allylestrone	+115.3°	+357	282	2140
Estradiol	+80°	+227	280	2140
2-Methylestradiol	+78°	+232	284	2400
2-Allylestradiol	+88°	+275	284	3090
2-Propylestradiol	+76.6°	+241	284	2820
4-Methylestradiol	—	—	280	1550
4-Allylestradiol	+44.3°	+138	282	1910
4-Propylestradiol	+31.2°	+98	282	1520

Data for estrone, estradiol and their 2-methyl derivatives are from the paper by Iriarte and Ringold,[18] and that for 4-methylestradiol from Dannenberg *et al.*[19]

EXPERIMENTAL[20]

Estrone allyl ether (I) was prepared as previously described,[2] except that allyl chloride and potassium iodide were used in place of allyl bromide. The yield was 88% of material with m.p. 106–107° (reported[2,3] m.p. 108–109°), λ_{max} 278–280 and 288 mμ (ϵ 2090 and 1910) ν_{max} 1745 (C=O) 1620 (isolated C=C), 1580 and 1495 (aromatic C=C), 1248 (ether), 915 (CH=CH_2), 873, and 811 cm.$^{-1}$ (two adj. ring H's).

2-Allyl-(II) *and 4-allylestrone* (III). A solution of estrone allyl ether (22.0 g.) in diethylaniline (175 ml.) was heated under reflux in a stream of nitrogen for 10 hr. The cooled solution was diluted with ether (2.0 l.) and washed with 10% hydrochloric acid (3 × 500 ml.), followed by water until neutral. The dried solution was evaporated to an oil which was chromatographed in benzene on silica (800 g.). Development with benzene, followed by elution with ether-benzene (1:19) gave crystalline fractions of m.p. varying from

(16) For weakly interacting substituents the intensity is vectorially additive and is proportional to the transition moment. Calculations by A. L. Sklar, *Rev. Modern Phys.*, **14**, 232 (1942) predicted an increased intensity for 1,2,4-trichlorobenzene and a reduced intensity for 1,2,3-trichlorobenzene as compared with *o*-dichlorobenzene, in full agreement with experimental results.

(17) H. Conrad Billroth *Z. Physik Chem.*, **629**, 170 (1935).

(18) J. Iriarte and H. J. Ringold, *Tetrahedron*, **3**, 28 (1958).

(19) H. Dannenberg, C. H. Doering, and D. Dannenberg-von Dresler, *Z. Physiol Chem.*, **317**, 174 (1959).

(20) All melting points are corrected. Optical rotations were measured as 1% solutions in dioxane at 25°. Ultraviolet absorption spectra were measured in ethanol using a Beckman DK 2 spectrophotometer. Infrared absorption spectra were determined in KBr disks in a Perkin-Elmer Model 21 spectrophotometer, equipped with sodium chloride optics. Thanks are expressed to Dr. J. Matthews and his staff for these determinations. Microanalyses were performed by A. Bernhardt, Müllheim, Ruhr, W. Germany.

145–155° to 110–115°. These were combined and separated by slow crystallization from ether-hexane at room temperature to give first *2-allylestrone* (II) (4.70 g.), separating in plates, m.p. 186–187°[21] (reported[3] m.p. 186–187°), $[\alpha]_D$ +152.2° λ_{max} 284–286 mμ (ε 3020), ν_{max} 3300 (bonded OH), 3090 (CH=CH_2), 1725 (C=O), 1640 (CH=CH_2), 1618, 1592 and 1511 (aromatic C=C), 917 (CH=CH_2), 896, 877 (isolated ring H), 830 and 822 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.22; H, 8.44; O, 10.31. Found: C, 81.25; H. 8.45; O, 10.63.

The *benzoate*, prepared with benzoyl chloride in pyridine, formed colorless plates, m.p. 194–195° from methanol-acetone, $[\alpha]_D$ +119.2°, λ_{max} 226 and 270 mμ (ε 21,400 and 3390).

Anal. Calcd. for $C_{28}H_{30}O_3$: C, 81.13; H, 7.30; O, 11.58. Found: C, 81.09; H, 7.34; O, 11.70.

Further crystallization of the rearrangement product gave *4-allylestrone* (III) (14.4 g.), separating in rosettes of flat, broad needles, m.p. 130–132°, raised by further crystallization to m.p. 136–137° (reported[3] m.p. 131–132°), $[\alpha]_D$ +115.3°, λ_{max} 282 mμ (ε 2140), ν_{max} 3300 (bonded OH), 3010 (CH=CH_2), 1725 (C=O), 1641 (CH=CH_2), 1593 and 1492 (aromatic C=C), 904 (CH=CH_2), 884, 865, 820 and 814 cm.$^{-1}$ (2 adj. ring H's).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.22; H, 8.44; O, 10.31. Found: C, 81.24; H, 8.51; O, 10.50.

The *benzoate*, prepared as for that of II, formed colorless needles, m.p. 165–166°, from methanol-acetone, $[\alpha]_D$ +84.6°, λ_{max} 224 and 275 mμ (ε 20,100 and 2140).

Anal. Calcd. for $C_{28}H_{30}O_3$: C, 81.13; H, 7.30; C, 11.58. Found: C, 81.31; H, 7.24; O, 11.62.

A 3:1 mixture of the benzoates of III and II melted at 155–160°. Reported[3] m.p. 155–160°.

2-Allylestradiol (IV). A solution of sodium borohydride (500 mg.) in water (15 ml.) was added to a solution of 2-allylestrone (500 mg.) in methanol (50 ml.). The solution was allowed to stand overnight, and then neutralized with acetic acid. The crystalline product was collected, washed well with water, and dried to give 435 mg. (85.7%) of *2-allylestradiol*, m.p. 81–83°. A sample recrystallized from aqueous methanol had m.p. 82–84°, $[\alpha]_D$ +88.1°, λ_{max} 284 mμ (ε 3090), ν_{max} 3330 (bonded OH), 1640 (CH=CH_2), 1619, 1586 and 1503 (aromatic C=C), 914 (CH=CH_2), 880 (isolated ring H) and 828 cm.$^{-1}$

Anal. Calcd. for $C_{21}H_{28}O_2$: 1/2, H_2O: C, 78.45; H, 9.09; O, 12.45. Found: C, 78.51; H, 9.06; O, 11.92.

4-Allylestradiol (V). 4-Allylestrone (500 mg.) in methanol (30 ml.) was reduced with sodium borohydride (500 mg.) in water (15 ml.) as described above. The product began to separate as fine needles after 1 hr. After being allowed to stand overnight, the solution was neutralized with acetic acid, and the product was collected, washed with water and dried to give 456 mg (90.7%) of (V), m.p. 90° and 137°. The analytical sample was crystallized from aqueous methanol to m.p. 90–91° and 140° (double m.p.), $[\alpha]_D$ +44.3°, λ_{max} 282 mμ (ε 1910), ν_{max} 3340–3150 (bonded OH), 1638 (CH=CH_2), 1594 and 1479 (aromatic C=C), 905 (CH=CH_2), 859 and 812 cm.$^{-1}$ (two adjacent ring H's).

Anal. Calcd. for $C_{21}H_{28}O_2$ 1/2 H_2O: C, 78.45; H, 9.09; O, 12.45. Found: C, 78.49; H, 8.93; O, 12.33.

2-Propylestradiol (VI). A solution of 2-allylestradiol (700 mg.) in ethanol (50 ml.) was hydrogenated over Adam's catalyst (35 mg.) at room temperature and atmospheric pressure. When hydrogen uptake was complete, the solution was filtered and evaporated to give a crystalline residue which when crystallized from cyclohexane gave pure *2-propylestradiol* (590 mg.; 83.8%), m.p. 89–91°, $[\alpha]_D$ +76.6°, λ_{max} 284 mμ (ε 2820), ν_{max} 3320 (bonded OH), 1618, 1591 and 1512 (aromatic C=C) and 867 cm.$^{-1}$ (isolated ring H).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.19; H, 9.62; O, 10.18. Found: C, 80.29; H, 9.28; O, 10.25.

4-Propylestradiol (VII). A solution of 4-allylestradiol (250 mg.) in ethanol (25 ml.) was hydrogenated over Adams' catalyst (25 mg.) as described above. Hydrogen uptake was rapid and complete in 1 hour. Crystallization of the crude product from cyclohexane gave 193 mg. (76.7%) of *4-propylestradiol*, m.p. 94–94.5°, $[\alpha]_D$ +31.2°, λ_{max} 282 mμ (ε 1520), ν_{max} 3340 (bonded OH), 1593 and 1490 (aromatic C=C) and 811 cm.$^{-1}$ (2 adj. ring H's).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.19; H, 9.62; O, 10.18. Found: C, 80.34; H, 10.06; O, 9.42.

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(21) The homogeneity of all compounds was established by paper chromatograms run in hexane-benzene on formamide impregnated Whatman No. 1 paper, using iodine-potassium iodide reagent. In this system, II was more mobile than III and all other compounds had the expected mobility ratios.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A.]

Steroids. CLXXVII.[1] New Approaches to C-11 Oxygenated 19-Norpregnanes[2]

A. BOWERS, J. S. MILLS, C. CASAS-CAMPILLO, AND CARL DJERASSI

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C-11 Hydroxylation of 19-norprogesterone (I) with *Rhizopus nigricans* (ATCC No. 6227b) or *Curvularia lunata* (Syntex strain 192) led to the corresponding 11α- and 11β-hydroxy analogs IIa and IIb, respectively. Microbiological dehydrogenation of the corresponding C-11 ketone (IIc) smoothly afforded the ring-A phenol (IVb). An alternate chemical synthesis of the benzoate of IVb is described which unequivocally establishes the structure assigned to the microbiological hydroxylation products.

The clinical importance of 19-nor steroids such as 19-nor-17α-methyltestosterone,[3] 19-nor-17α-ethinyltestosterone,[3] and the $\Delta^{5(10)}$-isomer[4] of the latter is now well recognized.[5] These substances are all

(1) Steroids. CLXXVI, P. G. Holton, *J. Org. Chem., in press.*

(2) A preliminary announcement of part of this work has been published; A. Bowers, C. Casas-Campillo, and C. Djerassi, *Tetrahedron*, **2**, 165 (1958).

(3) C. Djerassi, L. Miramontes, G. Rosenkranz, and F. Sondheimer, *J. Am. Chem. Soc.*, **76**, 4092 (1954); Abstracts, American Chemical Society Meeting, Milwaukee, April 1952, p. 18J.

(4) F. B. Colton, U. S. Patent **2,725,389.**

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