2-Epitetrahydroivalin. A solution of 0.25 g. of dehydrotetrahydroivalin in 20 ml. of 95% ethanol was allowed to stand with 0.04 g. of sodium borohydride for several hours. A few drops of acetic acid were added, solvent was removed at reduced pressure, and the residue diluted with water, made slightly alkaline with sodium bicarbonate, and extracted with benzene. The benzene extracts yielded 0.27 g. of solid, m.p. 157–166°. By crystallization from benzene, there was obtained 0.16 g. of 2-epitetrahydroivalin, m.p. 168–170°. Further recrystallization did not change the m.p. The mother liquors were chromatographed over 6 g. of acid-washed alumina, eluent benzene-chloroform (7:3). The first fraction consisted of 0.07 g. of slightly less pure 2-epitetrahydrovalin, m.p. 165–168° (total yield 0.23 g. or 92%), the second fraction was 0.02 g. (8%) of slightly impure tetrahydroivalin, m.p. 141–144°. 2-Epitetrahydroivalin had $[\alpha]^{26}D$ +29° (*c*, 4.5, $CHCl_3$), infrared bands at 3600, 3500 and 1770 $cm.^{-1}$

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59; O, 19.02. Found: C, 71.73; H, 9.40; O, 19.29.

2-Chlorotetrahydroalantolactone. A solution of 0.37 g. of tetrahydroivalin in 5 ml. of pyridine was treated with 0.3 ml. of phosphorus oxychloride and allowed to stand at room temperature for 24 hr. The mixture was poured over ice and the precipitate, wt. 0.27 g., recrystallized from ethanol, m.p. 160–162°, $[\alpha]^{26}D$ + 95.5° (*c*, 3.2, $CHCl_3$). The analysis indicated that the substance was contaminated by a small amount of olefin.

Anal. Calcd. for $C_{15}H_{23}O_2Cl$: C, 66.90; H, 8.53; O, 11.81; Cl, 13.09. Found: C, 67.42; H, 8.87; O, 11.44; Cl, 12.60.

Acknowledgment. Thanks are due Professor R. K. Godfrey, his students and Dr. Norlan Henderson for plant collections, Dr. Michael O'Dwyer for the rotatory dispersion curves and Drs. J. Schreiber and A. Eschenmoser for the oxidation rate measurements. The NMR spectrometer used in this research was purchased with funds provided by the Molecular Biophysics Institute at Florida State University.

TALLAHASSEE, FLA.

[CONTRIBUTION FROM THE SECTION OF EXPERIMENTAL MEDICINE, THE UNIVERSITY OF TEXAS M. D. ANDERSON HOSPITAL & TUMOR INSTITUTE]

Estrogens. IV. The Synthesis of 2- and 4-Alkylestrones[1-3]

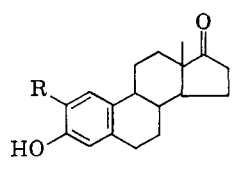
TAD L. PATTON

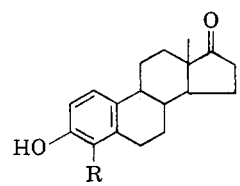
Received August 25, 1961

The synthesis of 2- and 4-alkylestrones *via* the Claisen rearrangement of estrone 3-allyl ether and estrone 3-crotyl ether is reported. The structural assignments are based on the infrared and ultraviolet spectra of the products and their mononitro derivatives.

During an investigation concerned with the effect of structural changes on the estrogenic activity of estrone, it was desirable to synthesize several 2- and 4-alkylestrones in which the alkyl groups were larger than methyl. The Claisen rearrangement of estrone allyl ether (I) offered a convenient method to synthesize these compounds. Although Miescher and Scholz reported this reaction, the only crystalline product described was a benzoate which was identified as the benzoate of 2- or 4-allylestrone.[4] The separation and identification of the two isomers formed during this rearrangement were reported recently in a brief communication.[5] It is the purpose of this paper to record this work in greater detail, to submit additional data in support of the structural assignments which were originally made on the basis of infrared spectra, to report the synthesis of other steroids from these products, and to describe the product which was formed during the Claisen rearrangement of the crotyl ether of estrone.

When a solution of I in diethylaniline was heated at reflux temperature in an atmosphere of nitrogen, two isomeric phenolic products were formed. They were separated by chromatography on a column of alumina. The higher melting isomer, 2-allylestrone (II), was eluted with benzene; then the second product, 4-allylestrone (III), was eluted with a solution of 9 parts benzene and 1 part ether. About 35% of unrearranged I was recovered; the yields of the products based on unrecovered ether were 28% II and 58% III. Each of the isomeric allylestrones formed a monoacetate.





II. R = CH_2=CH—CH_2— III. R = CH_2=CH—CH_2—
IV. R = CH_3—CH_2—CH_2— V. R = CH_3—CH_2—CH_2—

The hydrogenation of II over 5% palladium-on-charcoal gave 2-*n*-propylestrone (IV) in 80–85% yields. Similarly, III was hydrogenated to 4-*n*-propylestrone (V) in 75–80% yields. While

(1) Part III of this series appeared in *J. Org. Chem.*, **26**, 1677 (1961).

(2) This work was supported by grants CY-2873 and CY-5235 from the National Cancer Institute, U. S. Public Health Service.

(3) Presented before the Division of Medicinal Chemistry, American Chemical Society, 139th National Meeting, St. Louis, Mo., March 1961.

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

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

absorption bands at 3.26 μ (characteristic of the vinyl methylene group) and at 6.08 μ (characteristic of a nonconjugated carbon-carbon double bond) were observed in the infrared spectra of the allylestrones II and III, they were not present in the spectra of the hydrogenated products IV and V. Evidence that the carbonyl group at C-17 did not undergo reduction during the hydrogenation was provided by the infrared spectra of compounds IV and V which showed absorption bands at 5.75–5.76 μ (characteristic of C-17 carbonyl) and by the fact that both products reacted with acetic anhydride in the presence of pyridine to form monoacetates.

Initially the structural assignments given to II and III, and consequently IV and V, were based only on the following infrared absorption data (Table I). 1,2,4,5-Tetrasubstituted benzenes

TABLE I

INFRARED ABSORPTION MAXIMA (μ) OF 2- AND 4-ALKYLESTRONES

Compound	Isolated Ar-ring H	Adjacent Ar-ring H
II	11.16, 11.40	—
IV	11.16, 11.45	—
2-Methylestrone	11.35, 11.54	—
III	—	12.29
V	—	12.25
4-Methylestradiol[a]	—	12.28

[a] See footnote 8.

absorb in the 11.10–11.60-μ range[6]; 2-methylestrone which is an example of this type of substituted aromatic compound absorbs at 11.35 and 11.54 μ.[7] Since the infrared spectra of the higher melting allylestrone and its hydrogenation product also showed absorption in this range, it is reasonable to assigd them the structures of 2-allylestrone (II) and 2-*n*-propylestrone (IV), respectively. Although these absorption maxima are also present in the spectra of 1-substituted estrogens,[8] the Claisen rearrangement of I would not yield a product with this structure because it would involve the unlikely migration of the allyl group to a *meta* position.[9] A strong absorption band between 11.62 and 12.50 μ is characteristic of 1,2,3,4-tetrasubstituted benzenes[6] of which 4-substituted estrogens are an example. Since III and V exhibited a strong absorption maximum in this range, the alkyl substituent in each compound was assigned to position 4.

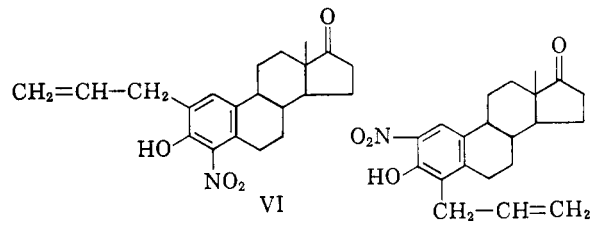
(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., John Wiley & Sons, Inc., New York, 1958, pp. 78–79.

(7) T. L. Patton, *J. Org. Chem.*, **25**, 2148 (1960).

(8) H. Dannenberg, C. H. Doering, and D. Dannenberg-von Dresler, *Z. Physiol. Chem.*, **317**, 174 (1959). The absorption maxima of several 1,3-, 2,3-, and 3,4-disubstituted 1,3,5(10)-estratrienes are reported.

(9) D. S. Tarbell, *Org. Reactions*, **2**, 1 (1949).

Additional evidence for these structural assignments was obtained from the nitration products of II and III. The nitration of II in glacial acetic acid at room temperature gave a mononitrophenolic product, 2-allyl-4-nitroestrone (VI). Although the melting point of VI was essentially the same as II, it was markedly depressed when the two were mixed. Mononitration of III under the same conditions gave 2-nitro-4-allylestrone (VII).



VI

VII

Pickering and Werbin observed during their investigation of the infrared spectra of nitrated estrogens that strong intramolecular hydrogen bonding between the phenolic hydroxyl group and the nitro group occurs in 2-nitroestrone but not in 4-nitroestrone where steric hindrance by ring B presumably prevents the nitro group at C-4 from becoming coplanar with ring A.[10] The intensity of the O—H stretching absorption band of 4-nitroestrone was reported to be significantly lower than that of 2-nitroestrone. A similar difference was found between the spectra of VI and VII, but the magnitude was too small to render it significant and conclusive. Therefore, additional evidence was desirable.

The ultraviolet absorption spectra of 2-nitroestrone and 4-nitroestrone reflect the effect of steric inhibition of resonance more clearly. The absorption maximum of 4-nitroestrone appears at a shorter wave length and with a lower extinction coefficient than those of 2-nitroestrone (Table II). The ultraviolet spectra of VI and VII differ

TABLE II

ULTRAVIOLET ABSORPTION MAXIMA (mμ) OF NITROESTRONES IN 95% ETHYL ALCOHOL

Compound	$\lambda_{max}(\epsilon)$
2-Nitroestrone	292 (7530) 363 (3626)
VII	304 (8624) 370–371 (3467)
4-Nitroestrone	278 (1768)
VI	272 (2617)

in a similar way. Although the absorption maxima of all four compounds are shifted to longer wave lengths in the presence of sodium hydroxide (Table III), the extinction coefficients of the absorption peaks exhibited by 4-nitroestrone and VI are considerably lower than those exhibited by 2-nitroestrone and VII. This data clearly supports

(10) R. A. Pickering and H. Werbin, *J. Am. Chem. Soc.*, **80**, 680 (1958).

TABLE III

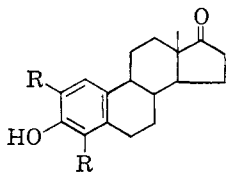
ULTRAVIOLET ABSORPTION MAXIMA (mμ) OF NITROESTRONES IN SODIUM HYDROXIDE

Compound	$\lambda_{max}(\epsilon)^a$
2-Nitroestrone VII	234 (18,563), 299 (6199), 438 (5297) 233 (22,191), 312 (6040), 456–458 (5615)
4-Nitroestrone VI	240 (11,685), 287 (2447), 429–430 (888) 243 (10,343), 291 (4377), 440 (1025)

[a] Solvent was 0.1*N* sodium hydroxide in 70% ethyl alcohol.

the structural assignments given to the products II and III, and consequently, IV and V.

2,4-Diallylestrone (VIII) was synthesized from a mixture of the allyl ethers of 2- and 4-allylestrones. The product underwent hydrogenation to give 2,4-di-*n*-propylestrone (IX).



VIII. R = CH_2=CH—CH_2—
IX. R = CH_3—CH_2—CH_2—

Estrone 3-crotyl ether (X) was prepared from estrone and crotyl chloride. Although an allylic rearrangement of the crotyl group was not expected to occur under the conditions of the reaction,[11] the following experiments were conducted to prove the identity of X. The ether X was hydrogenated to a product which was identical to an authentic specimen of estrone 3-*n*-butyl ether (XI) prepared from estrone and *n*-butyl iodide. Therefore, rearrangement did not occur and X was the desired estrone 3-crotyl ether. The infrared spectrum of X also supports this structural assignment. The isolated double bond in X absorbs at 5.94 μ which is characteristic of the C=C stretching vibrations of a CHR^1=CHR^2 type double bond.[12] If an allylic rearrangement had occurred during etherification then the double bond would have been terminal and would have been expected to absorb between 6.04 and 6.08 μ (1655–1645 $cm.^{-1}$).

When X was submitted to the Claisen rearrangement only one product was isolated. It exhibited absorption at 11.14 and 11.42 μ which is characteristic of 2-substituted estrones; therefore, it was assigned the structure of 2-(α-methylallyl)estrone (XII). Since the infrared spectra of neither the crude product from the Claisen rearrangement nor any of the fractions eluted from the chromatographic column exhibited absorption in the 12.0–12.5 μ region, characteristic of 4-substituted estrogens, it was concluded that no rearrangement to this position occurred. Fisher-Taylor-Hirschfelder models indicate that there is considerable steric hindrance by the hydrogen atoms at position 6 to the crotyl group in X and that there would be no relief of the steric strain by the rearrangement of X to 4-(α-methylallyl)estrone. This offers an explanation for the exclusive formation of XII during the rearrangement of X. There are reports in the literature which indicate that this observation is not unique. The allyl group in 3-methylphenyl allyl ether is reported to rearrange to positions 2 *and* 6[13] while the β-methylallyl group in β-methylallyl ethers of 3-methylphenol and 3,4-dimethylphenol rearrange exclusively to position 6.[14]

The biological properties of these compounds and other estrogens will be the subject of a future publication.

EXPERIMENTAL[15,16]

Estrone 3-allyl ether (I). The procedure of Miescher and Scholz[4] was used; the yield was 87%. Recrystallization raised the melting point to 108–109° (lit.,[4] m.p. 108–109°).

2-Allylestrone (II) *and 4-allylestrone* (III) *via the Claisen rearrangement of* I. A solution of I (3.5 g.) in 25 ml. diethylaniline was heated in a nitrogen atmosphere at reflux temperature for 6 hr. The cooled solution was taken up in 300 ml. ether and washed exhaustively with 4*N* hydrochloric acid to remove the diethylaniline. After washing the ether phase with water, it was dried over anhydrous sodium sulfate. The ether was evaporated and the oily residue was taken up in 30 ml. benzene and put on a column of acid-washed alumina (Merck). Elution of the column with benzene removed first unrearranged starting material (1.05 g.; 35% recovery) and then II (545 mg.; 28% yield based on unrecovered starting material). A solution of 9 parts benzene and 1 part ether was used to elute III (1.13 g., 58% yield based on unrecovered starting material). After two recrystallizations the two products had the following properties: *2-Allylestrone* (II) melted at 186–187°; $\lambda_{max}^{C_2H_5OH}$ 284 mμ (ε 2967); λ_{max}^{KBr} 2.96 (OH), 3.26 (vinyl CH_2), 5.77 (carbonyl), 6.08 (isolated C=C), 6.16, 6.26, and 6.66 (aromatic C=C), and 11.16, 11.40 μ (isolated aromatic ring H).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 80.92; H, 8.60.

The acetate, *2-allylestrone acetate*, melted at 119.5–120°; $\lambda_{max}^{C_2H_5OH}$ 270 mμ (ε 1151) and 278 mμ (ε 1218).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.00. Found: C, 78.20; H, 7.84.

4-Allylestrone (III) melted at 131–132°; $\lambda_{max}^{C_2H_5OH}$ 281 mμ (ε 2204); λ_{max}^{KBr} 2.98 (OH), 3.26 (vinyl CH_2), 5.77 (carbonyl), 6.08 (isolated C=C), 6.27 and 6.69 (aromatic C=C), and 12.29 μ (two adjacent aromatic ring H).

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.25; H, 8.44. Found: C, 81.02; H, 8.49.

(11) G. W. Wheland, *Advanced Organic Chemistry*, John Wiley & Sons, Inc., New York, 1949, p. 537.

(12) See footnote 6, p. 36.

(13) L. Dúbravková, I. Ježo, P. Šefčovič, and Z. Votický, *Chem. zvesti*, 12, 24 (1958). *Chem. Abstr.*, 52, 13665 (1958).

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

(15) Melting points were taken on a Fisher-Johns block and are uncorrected. A Beckman Model DU spectrophotometer with a photomultiplier attachment was used for all ultraviolet spectra measurements. The infrared spectra were recorded with a Perkin-Elmer Model 21 infrared spectrophotometer using a sodium chloride prism.

(16) The microanalyses were performed by The Laboratory of Microchemistry, Dr. Carl Tiedcke, Teaneck, N. J.

The acetate, *4-allylestrone acetate*, melted at 104–104.8°; $\lambda_{max}^{C_2H_5OH}$ 267 mμ (ε 438).

Anal. Calcd. for $C_{23}H_{28}O_3$: C, 78.37; H, 8.00. Found: C, 78.09; H, 7.81.

2-n-Propylestrone (IV). A suspension of 10% palladium-on-charcoal catalyst (200 mg.) in 75 ml. ethanol was saturated with hydrogen in a Parr hydrogenator at 60 p.s.i.g. for 1 hr. at room temperature. Then a solution of 2-allylestrone (375 mg.) in 25 ml. ethanol was added and shaking continued at 60 p.s.i.g. for 2 hr. The product was isolated in the usual way, and it was recrystallized from ethanol to give 300 mg. (80% yield); m.p. 189–192°. A second recrystallization from ethanol gave an analytically pure product, m.p. 192.5–193°; $\lambda_{max}^{C_2H_5OH}$ 284 mμ (ε 2924); λ_{max}^{KB} 2.95 (OH), 5.76 (carbonyl), 11.16 and 11.45 μ (isolated aromatic ring H).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.72; H, 9.03. Found: C, 80.82; H, 8.85.

It formed a *monoacetate*, m.p. 111°.

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 77.92; H, 8.53. Found: C, 77.79; H, 8.26.

4-n-Propylestrone (V). The procedure used for the hydrogenation of 4-allylestrone (300 mg.) over 10% palladium-on-charcoal catalyst (200 mg.) in 100 ml. ethanol was the same as that used for the hydrogenation of 2-allylestrone. The crude product weighed 240 mg. (80% yield), m.p. 173–174°, was recrystallized from ethanol to give an analytically pure product melting at 174–175°; $\lambda_{max}^{C_2H_5OH}$ 281 mμ (ε 1905); λ_{max}^{KBr} 2.95 (OH), 5.75 (carbonyl), 12.25 μ (two adjacent aromatic ring H).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.72; H, 9.03. Found: C, 80.44; H, 9.12.

It formed a *monoacetate*, m.p. 128–129°.

Anal. Calcd. for $C_{23}H_{30}O_3$: C, 77.92; H, 8.53. Found: C, 77.84; H, 8.36.

2-Allyl-4-nitroestrone (VI). To a solution of II (200 mg.; 0.00064 mole) in 4 ml. glacial acetic acid was added 0.041 ml. (0.00064 mole) nitric acid (sp. gr. 1.42) at room temperature. It was left at room temperature overnight and then poured into ice and water. The product was taken up in ether and the ether solution washed with 1*N* sodium hydroxide. This removed the more acidic VI from unchanged II. The alkaline solution was acidified and the product extracted with ether. It was isolated from the ether in the usual way. After chromatography on alumina a yield of 92 mg. of pure VI was isolated; m.p. 185–186°; $\lambda_{max}^{C_2H_5OH}$ 272 mμ (ε 2617); λ_{max}^{KBr} 3.0 (weak and broad, OH), 3.24 (vinyl CH_2), 5.75 (carbonyl), 6.06 (isolated C=C), 6.19, 6.29, and 6.60 (shoulder) (aromatic C=C), and 6.54 μ (NO_2).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C. 70.89; H, 6.88; N, 4.02.

2-Nitro-4-allylestrone (VII). The procedure was the same as that used for the synthesis of VI; however, chromatography was not necessary. From III (200 mg.; 0.00064 mole) was obtained 110 mg. of VII, m.p. 76–78°, after recrystallization from ethanol. An analytical sample melted at 77–78°; $\lambda_{max}^{C_2H_5OH}$ 220 mμ (ε 16,292), 304 mμ (ε 8624), and 370–371 mμ (ε 3467); λ_{max}^{KBr} 2.89 (OH), 3.25 (vinyl CH_2), 5.72 (carbonyl), 6.07 (isolated C=C), 6.16, 6.30, 6.60 (shoulder) (aromatic C=C), and 6.54 μ (NO_2).

Anal. Calcd. for $C_{21}H_{25}NO_4$: C, 70.96; H, 7.09; N, 3.94. Found: C, 71.22; H, 7.09; N, 3.74.

2,4-Diallylestrone (VIII). A mixture (1 g.) of 2-allylestrone and 4-allylestrone was dissolved in 10 ml. of a solution of sodium ethoxide which had been prepared from 10 ml. absolute ethyl alcohol and sodium metal (150 mg.). Then allyl bromide (3 ml.) was added, and the solution was heated at reflux temperature for 3 hr. The product was isolated in the usual way; it was a viscous oil. No attempt was made to isolate a crystalline product. The infrared spectrum of its solution in carbon tetrachloride showed the complete absence of absorption in the 3-μ region; this was proof of complete etherification.

The mixed allylestrone allyl ethers were dissolved in 10 ml. of dimethylaniline and heated at 190° for 18 hr. under nitrogen. Isolation of the product was achieved by the procedure used for II and III. The crude 2,4-diallylestrone, m.p. 113–116°, weighed 680 mg. Recrystallization from ethanol gave an analytically pure sample, m.p. 121.5–122°; $\lambda_{max}^{C_2H_5OH}$ 283 mμ (ε 2109); λ_{max}^{KBr} 287 (OH), 3.26 (vinyl CH_2), 5.76 (17-carbonyl), 6.09 (isolated C=C), 6.20, 6.31, and 6.78 (aromatic C=C), and 11.03 μ (isolated Ar ring H).

Anal. Calcd. for $C_{24}H_{30}O_2$: C, 82.24; H, 8.62. Found: C, 82.06; H, 8.88.

2,4-Di-n-propylestrone (IX). A suspension of 10% palladium-on-charcoal (400 mg.) in 50 ml. ethanol was saturated with hydrogen in a Parr hydrogenator at 60 p.s.i.g. and room temperature for 1.5 hr. Then a solution of 2,4-diallylestrone (400 mg.) in 50 ml. ethanol was added and the suspension shaken at 60 p.s.i.g. for 3 hr. After removing the catalyst, the alcohol was evaporated at reduced pressure. The residue was taken up in hot ethanol and filtered. The crude product (350 mg.; 88% yield) crystallized from solution; it melted at 120–122°. A second recrystallization gave analytically pure 2,4-di-*n*-propylestrone, m.p. 122–122.5°; $\lambda_{max}^{C_2H_5OH}$ 283 mμ (ε 2060); λ_{max}^{KBr} 2.92 (OH), 5.77 (17-carbonyl), 6.18, 6.33, and 6.77 (aromatic C=C), 11.03 μ (isolated Ar ring H).

Anal. Calcd. for $C_{24}H_{34}O_2$: C, 81.30; H, 9.66. Found: C, 81.41; H, 9.51.

Estrone 3-crotyl ether (X). Dry estrone (8.1 g.; 0.03 mole) was dissolved in a solution of sodium ethoxide which had been prepared from sodium metal (0.806 g.; 0.035 g.-atom) and 50 ml. of absolute ethanol. Then freshly distilled crotyl chloride was added in five 1-ml. portions during a period of 1 hr. The solution was stirred at reflux temperature for 18 hr. The reaction solution was filtered hot to remove the salt which had formed during the reaction. Upon chilling the filtrate 5.75 g. of crude product, m.p. 100–103.5°, crystallized; the filtrate yielded a second crop weighing 2.14 g., m.p. 94–98°. The total yield was 81%. After three recrystallizations from ethanol an analytically pure specimen of estrone 3-crotyl ether was obtained, m.p. 107°; $\lambda_{max}^{C_2H_5OH}$ 278 mμ (ε 1926); λ_{max}^{KBr} 3.32 (C—H stretching in isolated double bond), 5.75 (carbonyl), 5.94 (C=C stretching in crotyl group), 6.18, 6.35, and 6.68 (aromatic C=C), 7.95 μ (C—O—Ar).

Anal. Calcd. for $C_{22}H_{27}O_2$: C, 81.69; H, 8.41. Found: C, 81.69; H, 8.33.

Estrone 3-n-butyl ether (XI). A. Estrone (1.35 g.; 0.005 mole) was dissolved in a solution of sodium ethoxide prepared from 20 ml. absolute ethanol and sodium metal (0.23 g.; 0.01 g.-atom). Then freshly distilled *n*-butyl iodide (1.84 g.; 0.01 mole) was added and the solution heated at reflux temperature overnight. The product was isolated in the usual way to give 1.19 g., m.p. 105–107.5°. Recrystallization raised the melting point to 107–107.5°; λ_{max}^{KBr} 5.74 (carbonyl), 6.17, 6.34, 6.67 (aromatic C=C) and 7.94 μ (Ar—O—C).

Anal. Calcd. for $C_{22}H_{30}O_2$: C, 80.93; H, 9.26. Found: C, 81.20; H, 9.19.

B. Compound X (200 mg.) was hydrogenated in ethanol (25 ml.) in the presence of 5% palladium-on-charcoal (100 mg.). After isolation of the product and recrystallization from ethanol, it weighed 93 mg.; m.p. 104–105°. A second recrystallization raised the melting point to 106.5–107.5°. The infrared spectrum was identical to that of XI prepared by Method A.

2-(α-Methylallyl)estrone (XII). A solution of estrone 3-crotyl ether (5.0 g.) in *N,N*-diethylaniline (60 ml.) was heated at reflux temperature in a nitrogen atmosphere for 12 hr. The product was isolated by the same procedure which was used to isolate the allyl estrones. The crude product was chromatographed on a column of acid-washed alumina; elution with benzene gave 2.9 g. (58% yield) of pure 2-(α-methylallyl)estrone; m.p. 206–208°. No other product was isolated. Recrystallization from benzene raised the melting point to 211.0–211.5°; $\lambda_{max}^{C_2H_5OH}$ 284 mμ

(ϵ 2780); λ_{max}^{NaOH} 245 mμ (ϵ 7352), and 303 mμ (ϵ 4168)[17]; λ_{max}^{KBr} 2.95 (OH), 3.26 (vinyl CH_2), 5.76 (carbonyl), 6.08 (isolated C=C), 6.16, 6.27, 6.61 (aromatic C=C), and 11.14 and 11.42 μ (isolated aromatic ring H).

Anal. Calcd. for $C_{22}H_{28}O_2$: C, 81.43; H, 8.69. Found: C, 81.49; H, 8.54.

The acetate, *2-(α-methylallyl)estrone acetate*, melted at 134.5°; λ_{max}^{KBr} 3.27 (vinyl CH_2), 5.67 (acetate carbonyl), 5.75 (carbonyl), 6.08 (isolated C=C), 6.67 (aromatic C=C), and 8.20–8.25 μ (acetate C—O).

Anal. Calcd. for $C_{24}H_{29}O_3$: C, 78.86; H, 7.99. Found: C, 78.79; H, 8.59.

Acknowledgment. The author gratefully acknowledges the technical assistance of Mrs. Sylvia Capetillo for the ultraviolet spectroscopic determinations.

HOUSTON 25, TEX.

(17) The solvent used for these measurements was 0.1*N* sodium hydroxide in 70% ethyl alcohol.

[CONTRIBUTION FROM MERCK SHARP & DOHME RESEARCH LABORATORIES, DIVISION OF MERCK & CO., INC.]

Alkylated Adrenal Steroids. Dexamethasone-17 Methyl Ether

J. H. FRIED AND A. N. NUTILE

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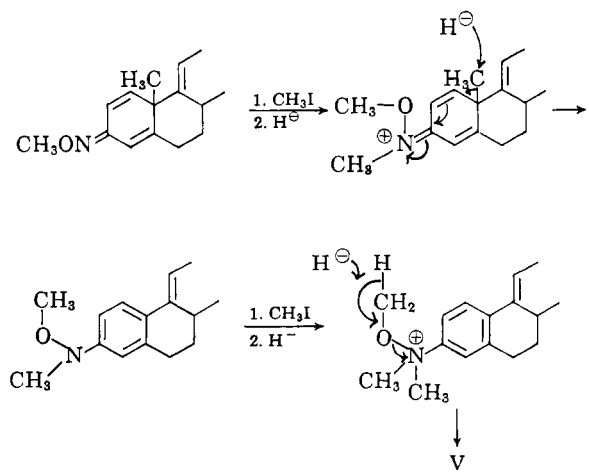
Dexamethasone-17 methyl ether has been prepared. Two A-ring aromatization reactions occurring during the course of the present work have been discussed, and the possible utility of the C-3 methoximes of 1,4-dienone-3-ones as base stable protecting groups has been indicated.

Since the biological effect of a 17-methoxy substituent in the anti-inflammatory series is unknown, it became of interest to prepare the 17-methyl ether (IX) of dexamethasone (9α-fluoro-16α-methyl - 1,4 - pregnadiene - 11β,17α,21 - triol-3,20-dione). A readily available synthetic intermediate was 16α-methyl-1,4,9(11)-pregnatriene-17α,21-diol-3,20-dione 21-acetate (I).[1] This compound was converted to the side chain protected C-20,21-acetonide (II). It was then necessary to find a protecting group for the A-ring dienone that would be able to withstand sodium hydride and methyl iodide in refluxing xylene, the conditions required to methylate the sterically hindered hydroxyl at C-17.

Although a number of base stable derivatives of C-3 ketones and enones in the steroid series are known, no convenient protecting group is available for the corresponding 1,4-diene-3-ones.[2] It was found that the dienone methoxime III was relatively stable under these methylating conditions and afforded the corresponding 17-methyl ether IV in 60% yield. In addition to IV, a more polar compound, V, was isolated in 4.5% yield. The analytical data obtained for compound V yielded the empirical formula $C_{27}H_{39}O_3N$. The infrared spectrum, λ_{max} 6.18 and 6.58 μ; ultraviolet spectrum,[3] λ_{max} 288, 317 mμ; E 24,500, 6300; and NMR spectrum:[4] four vinyl protons τ 2.45, 2.61 (H_1); 3.35, 3.51 (H_2); 3.67 (H_4); 4.07 (H_{11}) and two *N*-methyl groups τ 7.18; are in accord with structure V. The additional vinyl proton must arise during the aromatization reaction. Therefore, expulsion rather than migration of the angular methyl at C-19 must have occurred during the course of this transformation. A mechanism in accord with these facts can be written as follows:



(1) Unpublished results of Dr. R. Hirschmann of these laboratories. Obtained by mesyl chloride–pyridine dehydration of 16α-methylprednisolone 21-acetate. *Cf.* G. E. Arth, D. B. R. Johnston, J. Fried, W. W. Spooncer, D. R. Hoff, and L. H. Sarett, *J. Am. Chem. Soc.*, **80**, 3160 (1958). This compound was also converted to the corresponding 9β,11β-oxide. *Cf.* G. E. Arth, J. Fried, D. B. R. Johnston, D. R. Hoff, L. H. Sarett, R. H. Silber, H. C. Stoerk, and C. A. Winter, *J. Am. Chem. Soc.*, **80**, 3161 (1958). These compounds have also been reported by E. P. Oliveto, R. Rausser, L. Weber, A. L. Nussbaum, W. Gebert, C. T. Coniglio, E. B. Hershberg, S. Tolksdorf, M. Eisler, P. L. Perlman, and M. M. Pechet, *J. Am. Chem. Soc.*, **80**, 4431 (1958).

(2) *Cf.* L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, Reinhold Publishing Co., New York, 1959.

(3) A number of 3-methoxy-1,3,5(10), 9(11)-estratetraenes have ultraviolet absorption λmax 264, 299 mμ; E *ca* 18,000, 3000. L. Dorfman, *Chem. Revs.*, **53**, 129 (1953). A bathochromic shift of nitrogen compared to oxygen would not be unexpected.