and oxidized by procedure I. From 500 mg. of the diacetate XXVIII, 390 mg. of the quinone was isolated; m. p., alone and mixed with an authentic sample, 108–109°.

Acknowledgment.—The author is indebted to Dr. L. F. Fieser for his many helpful suggestions concerning this study, and to Margaret M. Racich for many of the analyses reported in these papers.

Summary

1. Several new methods for the preparation of 2-acyl-3-hydroxynaphthoquinones have been developed.

2. A new boron-trifluoride-catalyzed Thiele type of reaction has been found to take place between acetic anhydride and 2-acyl-1,4-naphthoquinones; the structures of the products have been elucidated.

3. The abnormal C-alkylation of a 2-acyl-1-naphthol type of compound with diazoethane has been investigated.

4. The reaction of 2-acetyl-3,4-diacetoxy-1-naphthol with a Grignard reagent has resulted in the preparation of two *cis–trans* isomeric olefins, whose ultraviolet absorption spectra were taken, and structural assignments based on these data were made.

5. The course of reduction of 2-acyl-3,4-diacetoxy-1-naphthol type compounds was investigated.

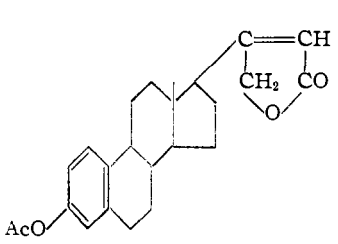
LOS ANGELES, CALIFORNIA RECEIVED MARCH 26, 1949

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

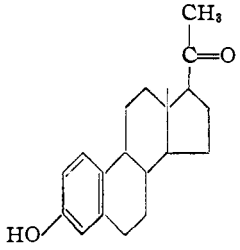
The Preparation of Two Aromatic Analogs of Desoxycorticosterone Acetate

BY CARL DJERASSI[1] AND CAESAR R. SCHOLZ

The biological testing of compounds containing both the nucleus of the estrogens and the functional side-chain of other physiologically active steroids is of considerable interest. Oettel[1a] reported on a pharmacological investigation of a cardiac aglucone derivative I, which contained an aromatic ring A, without disclosing the method of preparation, while Velluz and Muller[2] described the synthesis of an aromatic analog (II) of progesterone. The biological activity of the latter was unfortunately not indicated. The present paper summarizes our work on two independent syntheses of 3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III), as well as the preparation of the corresponding 1-methyl derivative XI. III and XI represent aromatic analogs of desoxycorticosterone acetate.



I



II

The starting material for the first synthesis (Flowsheet I) was 17-ethynylestradiol (IV), which has previously been converted[3] in unspecified yield by Rupe–Nickel reduction to 17-vinylestradiol (Va). The use of a palladium–calcium carbonate catalyst in pyridine solution[4] in the present instance led in 88% yield to the desired 17-vinyl derivative, which was converted into its methyl ether Vb with dimethyl sulfate. Hydroxylation of Vb with osmium tetroxide, followed by acetylation gave 50% of 3-methoxy-10-nor-1,3,5-pregnatriene-17,20,21-triol 20,21-diacetate (VI), which was subjected to a modified Serini reaction[5] in toluene solution and thus furnished directly the desired cortical hormone derivative III in 63% yield.

The aromatic analog III could also be prepared from methyl 3-ketoetiochola-1,4-dienate (VII) (Flowsheet II), which has been synthesized from cholesterol.[6] Aromatization with elimination of the angular methyl group of the dienone ester VII in tetralin solution at 650° by the general procedure of Inhoffen[7] led in 44% yield to the phenolic ester VIIIa which proved to be insoluble in 10% aqueous alkali. This methyl ester (VIIIa) as well as the 3-methyl ether 17-methyl ester (VIIIb) required drastic conditions for saponification (refluxing in 20% alcoholic potassium hydroxide solution for eighteen hours). This behavior is in marked contrast to the relative ease of saponification of the dienone ester VII or the aromatic

(1) Present address: Laboratorias Syntex, S. A., Laguna Mayran 413, Mexico City, D. F.

(1a) Oettel, *Pharmazie*, **2**, 385 (1947).

(2) Velluz and Muller, *Compt. rend.*, **226**, 411 (1948).

(3) Inhoffen, Logemann, Hohlweg and Serini, *Ber.*, **71**, 1024 (1938).

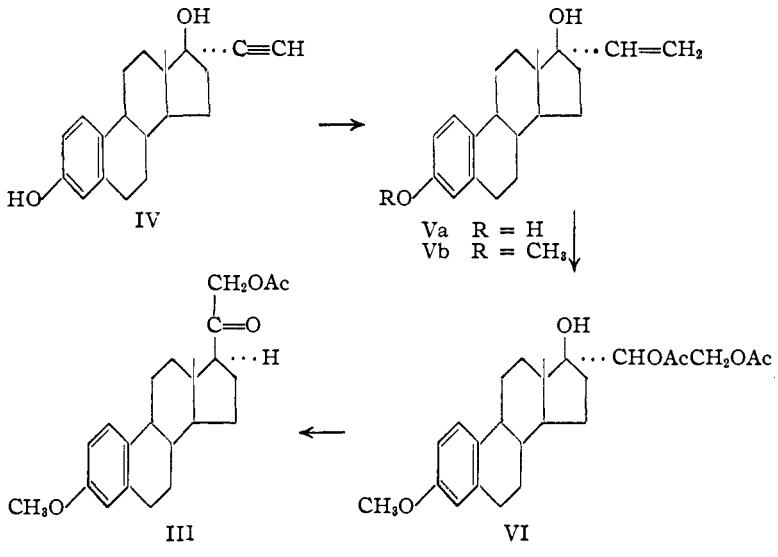
(4) Ruzicka and Müller, *Helv. chim. acta*, **22**, 755 (1939).

(5) Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd edition, Reinhold Publishing Corporation, New York, N. Y., 1949, pp. 440–444; see Miescher and Heer, U. S. Patent 2,372,841.

(6) Djerassi and Scholz, THIS JOURNAL, **69**, 2404 (1947).

(7) British Intelligence Objectives Sub-Committee F.I.A.T. Final Report No. 996, "The Commercial Development and Manufacture of Synthetic Hormones in Germany," H. M. Stationery Office, London, 1947, pp. 20 and 79; see also Inhoffen, *Angew. Chem.*, **59**, 207 (1947), and Wilds and Djerassi, THIS JOURNAL, **68**, 2125 (1946).

FLOWSHEET I



ester Xa,[6,8] which required only 5–10% alkali for *ca.* five hours. If it is assumed that the estrogens have a relatively planar all-*trans* configuration just as the other steroid hormones, then it is not possible to explain this anomalous behavior on steric grounds. An inversion at carbon atom 17 during the high temperature aromatization may be considered improbable, since the final product (III) in both syntheses proved to be the same.

The 3-methyl ether 17-carboxylic acid (VIIIc) was converted by the Wilds–Shunk procedure[9] to the acid chloride and thence to the crystalline diazoketone IX in 61% yield (based on VIIIc).

Decomposition in boiling acetic acid solution gave 56% of the ketol acetate III, which was shown to be identical with the specimen synthesized by the first procedure by analysis, rotation, mixed melting point determination, ultraviolet and infrared absorption spectra. The infrared spectra were taken in carbon disulfide solution and showed maxima at 1733 and 1756 cm.$^{-1}$ characteristic of the ketol acetate grouping.[10]

The configuration of the ethynyl group in 17-ethynylestradiol (IV) is generally believed to be α by analogy to the corresponding reaction in the androstane series[11] and since the Serini reaction is known to involve inversion,[5] the final product III should have the ketol side-chain in the β-configuration as is the case with the naturally occurring cortical hormones. The satisfactory agreement in the

FLOWSHEET II

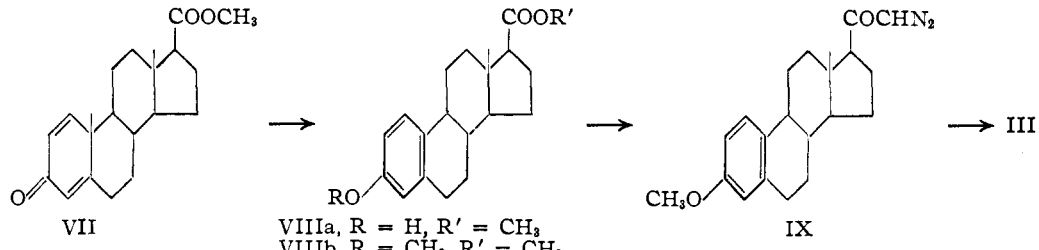


TABLE I

EVIDENCE FOR β-CONFIGURATION OF SIDE-CHAIN BY MOLECULAR ROTATION DIFFERENCES

Compound	$[\alpha]_D$ Anhydr. ethanol	$[M]_D$[a]	$\Delta[M]_D$
3-Methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III)	+160°	592	+372
3-Methoxy-1,3,5-estratriene[b]	+ 81°	220	
Desoxycorticosterone acetate[c]	+181°	673	+382
Δ^4-Androsten-3-one[d]	+107°	291	
17-Isodesoxycorticosterone acetate[e]	− 26°	−97	−388

[a] $[M]_D = [\alpha]_D \times$ mol. wt./100. [b] A. Butenandt, I. Störmer and U. Westphal, *Z. physiol. Chem.*, 208, 149 (1932). [c] In 95% ethanol, $[\alpha]^{25}D$ was +188°. [d] Kindly furnished by Dr. A. F. St. André of our laboratories. [e] C. W. Shoppee, *Helv. chim. acta*, **23**, 930 (1940); this rotation was determined in acetone solution.

(8) The 1-methyl-3-hydroxy-1,3,5-triene structure of the acid X and of all the other products arising from dienone-phenol rearrangements studied by us [THIS JOURNAL, **68**, 1712, 2125 (1946); **69**, 2404 (1947); **70**, 1911 (1948); *J. Org. Chem.*, **13**, 697, 848 (1948)] was assigned by analogy to an unequivocal case in the chrysene series [Wilds and Djerassi, THIS JOURNAL, **68**, 1715 (1946)] in which the structure of both the dienone and the rearrangement product was proven by total synthesis. Recent work in Prof. R. B. Woodward's laboratory at Harvard (private communication to C. D.) with simple model compounds has indicated that in the steroid series the following two structures are equally plausible: 1-methyl-4-hydroxy-1,3,5-triene or 1-hydroxy-4-methyl-1,3,5-triene. For simplicity's sake, the 1-methyl-3-hydroxy structure is used until unequivocal evidence is presented for an example in the steroid series.

(9) Wilds and Shunk, THIS JOURNAL, **70**, 2427 (1948); *cf.* also Djerassi, Scholz and Leathem, *Experientia*, **5**, 204 (1949).

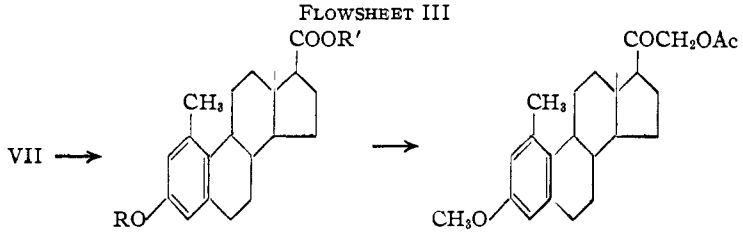
(10) Jones, Williams, Whalen and Dobriner, THIS JOURNAL, **70**, 2024 (1948).

(11) Ref. 5, p. 328.

calculation of the molecular rotation differences (Table I) lends considerable support to this statement.

The diazoketone synthesis was also employed in the preparation of the aromatic desoxycorticosterone analog XI with a methyl group at C-1[8] (Flowsheet III). Methyl 1-methyl-3-acetoxy-1,3,5-estratriene-17-carboxylate (Xa), previously obtained[6] in high yield by dienone–phenol rearrangement of VII, was converted to 1-methyl-3-methoxy-1,3,5-estratriene-17-carboxylic acid (Xb) in 76% over-all yield. Treatment of its acid chloride (prepared by the Wilds–Shunk procedure)[9] with diazomethane led to an oily diazoketone which on decomposition with acetic acid afforded the desired 1-methyl-3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (XI).

FLOWSHEET III



Xa, R = CH_3CO, R' = CH_3
Xb, R = CH_3, R' = H

XI

Preliminary results of the biological investigation by Dr. James H. Leathem of the Bureau of Biological Research, Rutgers University, indicate that the aromatic analogs III and XI of desoxycorticosterone acetate when administered in oil solution are inactive as estrogens in 1-mg. doses (uterine weight increase in rats) and do not maintain the life of adrenalectomized rats in 0.5-mg. doses (desoxycorticosterone acetate under the same conditions is effective at a 0.05-mg. level).

Acknowledgment.—The authors are indebted to the Misses Frances Hoffmann and Edwina Leathem for their capable assistance, to Miss Verda Powell for the rotations and ultraviolet absorption spectra and to Dr. A. F. St. André for furnishing the palladium catalyst and a sample of Δ^4-androsten-3-one. The infrared spectra were determined at the Sloan–Kettering Institute for Cancer Research, New York City, through the courtesy of Dr. K. Dobriner and Mrs. P. Humphries.

Experimental[12]

17-Vinylestradiol (Va).—A solution of 2.50 g. of 17-ethynylestradiol (IV)[8] in 50 ml. of C.P. pyridine was shaken at room temperature with hydrogen in the presence of 0.4 g. of 2% palladium–calcium carbonate catalyst.[1] After an initial lag of ten to thirty minutes, the hydrogen uptake proceeded smoothly and stopped after *ca.* forty minutes (one mole of hydrogen), whereupon the catalyst was filtered and solvent was removed *in vacuo*. Trituration with ether and hexane afforded 2.22 g. (88%) of colorless crystals with m. p. 142–147°, $[\alpha]^{25}D$ +59.5° (dioxane), which were satisfactory for the next step; lit.,[3] m. p. 148–150°, $[\alpha]D$ +57.3° (dioxane).

The 3-monoacetate crystallized in colorless prisms from hexane, m. p. 126–127.5°, $[\alpha]^{25}D$ +61.2° (dioxane).

Anal. Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.25; H, 8.19.

17-Vinylestradiol 3-Methyl Ether (Vb).—Methylation was accomplished by treating 2.22 g. of the above phenol (Va) in 50 ml. of ethanol over a period of ten minutes on the steam-bath four times alternately with 4-ml. portions each of 50% aqueous potassium hydroxide and dimethyl sulfate. The alkaline solution was heated for an additional ten minutes, then cooled and acidified with dilute acid. The precipitate (2.20 g., m. p. 90–95°) was collected and recrystallized from a mixture of hexane and acetone, whereupon it was obtained as colorless crystals with m. p. 98–100°, $[\alpha]^{25}D$ +60° (chloroform); yield 1.89 g. (82%).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03. Found: C, 80.84; H, 9.37.

3-Methoxy-10-nor-1,3,5-pregnatriene-17,20,21-triol 20,21-Diacetate (VI).—A mixture of 1.85 g. of the methyl ether Vb, 2 g. of osmium tetroxide and 160 ml. of anhydrous ether was allowed to stand in a closed flask at room temperature for five days. The ether was decanted and the black residue was refluxed for three and one-half hours with 50 ml. of ethanol, 100 ml. of water and 14 g. of sodium sulfite heptahydrate. After filtration and boiling of the precipitate repeatedly with ethanol, the combined extract and filtrate were concentrated, diluted with water, extracted with ether and the washed and dried ether solution was evaporated to a small volume. The colorless crystals (1.29 g., m. p. 136–143°) of the triol were filtered and directly acetylated by heating for three and one-half hours at 65° with 15 ml. of acetic anhydride and 25 ml. of pyridine. Evaporation of the solution to dryness under reduced pressure and trituration of the residue with hexane yielded 1.28 g. (50% over-all) of diacetate with m. p. 109–113°, which was satisfactory for the Serini reaction. The analytical sample, obtained from hexane, had m. p. 111–113°, $[\alpha]^{25}D$ +19° (chloroform).

Anal. Calcd. for $C_{25}H_{34}O_6$: C, 69.74; H, 7.96; methoxyl, 7.21; acetyl, 19.99. Found: C, 69.57; H, 8.02; methoxyl, 7.67; acetyl, 19.68.

3-Methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III) from Serini Reaction on Diacetate VI.—A solution of 400 mg. of the above diacetate VI in 80 ml. of dry toluene was refluxed for forty-eight hours with 8 g. of zinc dust, then filtered while still hot and the solvent removed under reduced pressure. The residue was chromatographed on 8 g. of dil. sulfuric-acid-washed alumina (Aluminum Company of America, Grade F-20, 80–200 mesh) and the product was eluted with a mixture of hexane and benzene (60/40). Recrystallization from hexane gave 215 mg. (63%) of colorless, prismatic needles of the ketol acetate III with the following physical constants: m. p. 118–119°, $[\alpha]^{25}D$ +157 ± 0.5° (chloroform), +160° (ethanol), maximum at 278 mμ (log *E* 3.39) and minimum at 246 mμ (log *E* 2.72); the infrared spectrum showed carbonyl peaks at 1733 and 1756 cm.$^{-1}$ typical of the cortical hormone side-chain.[10]

Anal. Calcd. for $C_{25}H_{30}O_4$: C, 74.56; H, 8.16; acetyl, 11.62; methoxyl, 8.38. Found: C, 74.79; H, 8.34; acetyl, 12.27; methoxyl, 8.85.

(12) All melting points are corrected unless noted otherwise. Rotations were determined on 5–10-mg. of sample in 1.2 ml. of solvent in a 1-dcm. polarimeter tube of 1-ml. capacity. All ultraviolet absorption spectra measurements were carried out in ethanol solution on a Beckman quartz photoelectric spectrophotometer, while the infrared spectra were measured in carbon disulfide solution at the Sloan-Kettering Institute on a Perkin-Elmer infrared spectrometer. The microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J.

(13) Busch and Stöve, *Ber.*, **49**, 1064 (1916).

Methyl 3-Hydroxy-1,3,5-estratriene-17-carboxylate (VIIIa).[14]—A 44% yield of material of satisfactory purity (m. p. 212–216°) was realized by using the same reaction conditions for the aromatization of methyl 3-ketoetiochola-1,4-dienate (VII)[6] as were reported by Inhoffen[7] for the conversion of 1,4-androstadien-17-ol-3-one to estradiol. Recrystallization from ethanol afforded colorless crystals of the methyl ester VIIIa; m. p. 219–220°, $[\alpha]^{24}D$ +107° (acetone), which exhibited the typical ultraviolet absorption spectrum of a phenol: maximum at 280 mμ (log E 3.39) and minimum at 247.5 mμ (log E 2.63).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; methoxyl, 9.87. Found: C, 76.29; H, 8.33; methoxyl, 9.61.

The 3-acetate 17-methyl ester (VIIIe), prepared by heating the phenol VIIIa for one hour with acetic anhydride and pyridine, was obtained as colorless needles from a mixture of hexane and acetone, m. p. 146–147.5°, $[\alpha]^{24}D$ +79.7° (acetone).

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; acetyl, 12.07. Found: C, 74.43; H, 7.73; acetyl, 12.37.

3-Hydroxy-1,3,5-estratriene-17-carboxylic Acid (VIIId).—The 3-hydroxy 17-methyl ester VIIIa could be saponified only with difficulty. When 150 mg. of the methyl ester was refluxed with 500 mg. of potassium hydroxide and 20 ml. of methanol for eighteen hours, less than 30% of the material was saponified. By contrast, the dienone ester VII was saponified readily under these conditions. Complete hydrolysis was accomplished by refluxing 100 mg. of the ester with either 1 g. of potassium hydroxide and 5 ml. of methanol, or 10 ml. of a hydrobromic acid–acetic acid mixture (30 ml. of glacial acetic acid, 20 ml. of 48% hydrobromic acid and 10 ml. of water)[15] for eighteen hours. The crude acid, which is readily removed from ether with sodium carbonate solution, although the sodium salt is not too soluble in water, melted at approximately 256–263° (dec., uncor.). After recrystallization from hexane–acetone, the following constants were observed: m. p. 270–274° (dec., uncor.), $[\alpha]^{25}D$ +98.4° (acetone), maximum at 280 mμ (log E 3.32) and minimum at 248 mμ (log E 2.81). A sample was dried at 120° under vacuum for twelve hours before analysis.

Anal. Calcd. for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05; neut. equiv., 300. Found: C, 76.37; H, 8.15; neut. equiv., 304.

Methyl 3-Methoxy-1,3,5-estratriene-17-carboxylate (VIIIb).—The methylation of the phenolic methyl ester VIIIa was carried out with dimethyl sulfate exactly as described for 17-vinylestradiol (Va) and afforded 94% of material of m. p. 160–163° suitable for the saponification step. The analytical sample crystallized from ethanol as long needles, m. p. 163–164°, $[\alpha]^{26}D$ +47.6° (chloroform).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; methoxyl, 18.90. Found: C, 76.57; H, 8.43; methoxyl, 18.93.

3-Methoxy-1,3,5-estratriene-17-carboxylic Acid (VIIIc).—The above ester VIIIb was saponified by refluxing 2.56 g. for eighteen hours with 25 g. of potassium hydroxide and 125 ml. of methanol. Acidification with dilute acid, followed by filtration and digestion with boiling ethanol gave 2.14 g. (87%) of the desired acid VIIIc with m. p. 217–218°. Recrystallization from ethanol raised the m. p. to 219–220°, $[\alpha]^{26}D$ +102° (dioxane).

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34; methoxyl, 9.87. Found: C, 76.56; H, 8.28; methoxyl, 10.05.

3-Methoxy-17-(β-diazoacetyl)-1,3,5-estratriene (IX).—Six hundred milligrams of the acid VIIIc was converted into the sodium salt by dissolving in hot ethanol, adding 80 mg. of sodium hydroxide and evaporating to dryness in a current of air. The nearly colorless sodium salt was dried at 100° and 30 mm. for eighteen hours and then suspended in 15 ml. of dry benzene and 3 drops of pyridine. Oxalyl chloride (3 ml.) was added while cooling in ice and after five minutes at 10°, the yellow solution was distilled to dryness at room temperature *in vacuo*. After adding benzene twice and evaporating, the residue was stirred with benzene, filtered through sintered glass and the nearly colorless filtrate was added to an undistilled ethereal solution of diazomethane (from 7.5 g. of nitroso methylurea) kept at −10° and previously dried for two hours over solid potassium hydroxide. After one hour in ice, the solvent was removed under reduced pressure at 20° and the solid residue was recrystallized from a mixture of hexane and acetone yielding 390 mg. (61%) of the light yellow diazoketone IX with m. p. 126–128° (gas evolution complete at 135°). Extremely slow burning was necessary to obtain even fair analytical results.

Anal. Calcd. for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 73.87; H, 7.96; N, 8.57.

3-Methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III) from the Diazoketone IX.—The solid diazoketone (390 mg.) was dropped slowly into 20 ml. of boiling glacial acetic acid[9] and heating was continued for an additional five minutes. The yellow solution was evaporated to dryness and the residue was chromatographed as described above yielding 240 mg. (56%) of the ketol acetate III with m. p. 113–115°, $[\alpha]^{25}D$ +158° (chloroform). Further recrystallization raised the m. p. to 117–118° and no depression was observed on admixture with a specimen prepared by the first method from 17-vinylestradiol. The ultraviolet and infrared spectra of the two samples were identical.

1-Methyl-3-methoxy-1,3,5-estratriene-17-carboxylic Acid (Xb).—A solution of 1.90 g. of the 3-acetoxy 17-methyl ester Xa[6] in 80 ml. of methanol was refluxed with 8 g. of potassium hydroxide for three hours and acidified. The precipitate was collected, dried and then treated in ether solution with diazomethane.[16] The solvent was removed after a few minutes, the residue was dissolved in ethanol and methylated with dimethyl sulfate in the presence of 50% aqueous potassium hydroxide solution as described previously. The crude 3-methoxy 17-methyl ester was not purified, but was saponified directly by refluxing with 5 g. of potassium hydroxide and 60 ml. of methanol for four hours. After dilution with water and extraction with ether, the alkaline solution was acidified, and afforded 1.27 g. (76%) of the desired 3-methoxy-17-carboxylic acid (Xb) melting at 237–245°. The analytical sample crystallized from acetone; m. p. 245–246°, $[\alpha]^{23}D$ +242° (chloroform), minimum at 251 mμ (log E 2.77) and broad maximum at 278–284 mμ (log E 3.32).

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59; methoxyl, 9.45. Found: C, 76.41; H, 8.47; methoxyl, 9.33.

1-Methyl-3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (XI).—The diazoketone synthesis was carried out exactly as described above for the acid VIIIc, except that the diazoketone was obtained as an oil, and was therefore treated with acetic acid without purification. The desired ketol acetate XI was obtained in 27% yield with m. p. 152–154° after crystallization from a mixture of hexane and acetone. Further recrystallization afforded rosettes of colorless prisms with m. p. 154–156°, $[\alpha]^{24}D$ +276° (chloroform). The infrared spectrum showed the characteristic peaks[10] at 1733 and 1756 cm.$^{-1}$, while the ultraviolet absorption spectrum exhibited a broad maximum at 278–284 mμ (log E 3.33), already observed with the precursor Xb, and a minimum at 248 mμ (log E 2.34).

Anal. Calcd. for $C_{24}H_{32}O_4$: C, 74.96; H, 8.39; acetyl, 11.19. Found: C, 74.72; H, 8.24; acetyl, 11.09.

Summary

Two syntheses of 3-methoxy-17-(β-acetoxyacetyl)-1,3,5-estratriene (III), an aromatic analog of desoxycorticosterone acetate, are described. The first procedure involved hydroxylation of 17-

(14) The identical methyl ester (mixed melting point determination) was isolated recently from strophanthidin by Ehrenstein and co-workers (*J. Org. Chem.*, in press).

(15) Johnson, Petersen and Schneider, THIS JOURNAL, **69**, 75 (1947).

(16) The intermediate methylation with diazomethane was essential for a good yield.

vinylestradiol methyl ether (Vb) with osmium tetroxide followed by acetylation and Serini reaction of the 20,21-diacetate (VI). The second method consisted of partial aromatization of ring A with the elimination of the angular methyl group of an appropriately substituted etiocholanic acid derivative (VII) and subsequent introduction of the ketol side-chain *via* the diazoketone.

The diazoketone synthesis was also employed in the preparation of an aromatic cortical hormone analog (XI) with a methyl group at C-1. Neither product showed estrogenic or life maintenance activity in rats at the dosage tested.

SUMMIT, NEW JERSEY RECEIVED JUNE 18, 1949

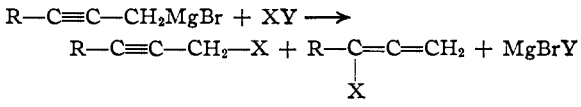
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF ANTIOCH COLLEGE]

Beta Acetylenic Grignard Reagents. I. Hydrolysis and Carbonation of γ-Phenylpropargylmagnesium Bromide

BY GERALD R. LAPPIN*

An earlier investigation of the reaction of β-acetylenic halides with magnesium[1] reportedly showed that no Grignard reagent was formed and only coupling occurred. It has now been found that certain of these halides do yield an organometallic derivative with magnesium, at least one, γ-phenylpropargyl bromide, giving an excellent yield under the ordinary conditions of this reaction.[2]

The structural similarity of β-acetylenic Grignard reagents to those derived from allylic halides led to the question of whether the former would undergo rearrangement similar to the well-known rearrangement of allylmagnesium halides, yielding both acetylenic and allenic products. Rearrangement of β-acetylenic compounds to allenes has been observed[3] but under conditions totally unlike those of the Grignard reaction. When it was found that these new organomagnesium compounds could be prepared it was decided to investigate this possible rearrangement. Because it required no special method and was obtained in high yield γ-phenylpropargylmagnesium bromide was chosen for this study[4] and the reactions chosen were hydrolysis and carbonation.



Discussion of Results

Hydrolysis.—The hydrolysis of γ-phenylpropargylmagnesium bromide (I) under oxygen and peroxide free conditions gave up to an 87% yield of monomeric hydrocarbon product. On distillation through a high efficiency fractionating column this gave phenylpropadiene (II) as well as 1-phenyl-1-propyne (III) along with a considerable amount of polymeric residue. Both products were identified by comparison with the previously reported characteristics, II being identified by its boiling point,[5,6] refractive index,[6] rapid polymerization[5,6] and rapid uptake of oxygen from the air to form a ketone, presumably methyl phenyl diketone.[5] Identification of III was made through its boiling point and refractive index.[7] Final confirmation was obtained from the oxidation of these hydrocarbons with potassium permanganate in pyridine solution,[8] II yielding only benzoic acid while III gave both benzoic and acetic acids.

An attempt was made to determine the ratio of acetylene to allene formed by oxidation followed by analysis for the ratio of benzoic to acetic acid formed.[8] Because of the rapid polymerization of II consistent results were not obtained, the amount of II present in the monomeric product ranging from 6 to 37% in various experiments. However, in those experiments which gave a low yield of monomeric II a high yield of polymer was obtained and if the polymer consisted only of phenylpropadiene this must have made up more than half of the total hydrolysis product. Since in at least one experiment practically no volatile monomer was obtained it is evident that copolymerization between II and III can occur so that any estimate of the composition of the total reaction mixture is very doubtful. It was clearly shown, nevertheless, that an allylic-like rearrangement did occur, whether during the formation of the organomagnesium bromide or during the subsequent hydrolysis it is, at present, impossible to say.

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(1) Lai, *Bull. soc. chim.*, **53**, 1543 (1933).

(2) Since the completion of the work herein described, Newman and Wotiz, THIS JOURNAL, **71**, 1292 (1949), have briefly mentioned the preparation in 95% yield of a Grignard reagent from 1-bromo-2-heptyne using a special "high dilution technique" which was not described. Carbonation was said to yield an unidentified mixture of acids. In this Laboratory the Grignard reagent has been prepared from 1-bromo-2-octyne in about 30% yield by a method which will be described in a subsequent publication.

(3) For a summary of such rearrangements see Johnson, "Acetylenic Compounds," Edward Arnold and Company, London, 1946, Vol. I, p. 63 ff.

(4) Later results have shown this choice to be a poor one for the phenylpropadiene derivatives polymerize much more rapidly than purely aliphatic allenic compounds. Further work on these rearrangements is being carried out with octynylmagnesium bromide.

(5) Bourguel, *Compt. rend.*, **192**, 686 (1931).

(6) Ginsberg, *J. Gen. Chem.* (*U. S. S. R.*), **8**, 1029 (1938).

(7) Truchet, *Ann. chim.*, **16**, 309 (1931).

(8) Young, Ballou and Nozaki, THIS JOURNAL, **61**, 12 (1939).