column at column temperature of 120°. One major peak was observed having the same retention time as an independently synthesized mixture[17,18] of the *cis*- and *trans*-β,γ esters. A peak amounting to 1% of the β,γ peak was also observed having the same retention time as the *trans*-α,β ester. When the photolysis was run in ethyl acetate this peak was not observed. That the main peak was indeed a mixture of the *trans*- and *cis*- β,γ isomers was shown by preparative tlc on $AgNO_3$–SiO_2 eluting several times with 1% ether–hexane. The *trans*-β,γ predominated by a factor of 2 over the *cis* and traveled closest to the solvent front. Both isomers were identified by comparing their infrared spectra with those of authentic samples, prepared independently.

Registry No.—**1** (*cis*), 15790-85-9; **1** (*trans*), 15790-86-0; **2** (*cis*), 15790-87-1; **2** (*trans*), 15790-88-2; **3** (*cis*), 4358-59-2; **3** (*trans*), 623-43-8; **4** (*cis*), 15790-91-7; **4** (*trans*), 334-49-6; **5** (*cis*), 15790-93-9; **5** (*trans*), 15790-94-0; **6** (*cis*), 2825-68-5; **6** (*trans*), 929-79-3.

(17) M. Newman and J. J. Wotiz, *J. Amer. Chem. Soc.*, **71**, 1292 (1949).
(18) R. P. Linstead, E. G. Noble, and E. J. Boorman, *J. Chem. Soc.*, 557 (1933).

A Concomitant Ethinylation and Esterification Reaction

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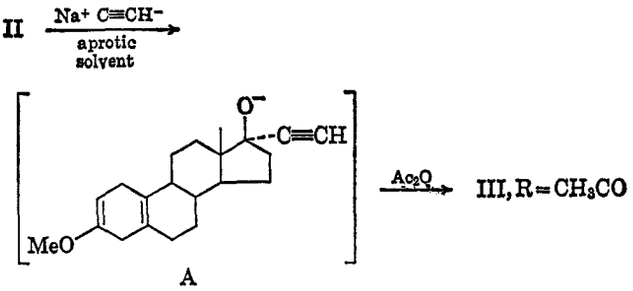
The preparation of 10β-hydroperoxy steroids, such as 10β-hydroperoxy-17α-ethinyl-17β-hydroxy-4-estren-3-one (I, R = H), has been reported from these laboratories.[1] Tests in rats have shown that I (R = H) is a potent contraceptive agent acting by a novel biological mechanism.[2] In view of the marked anticonception activity ascribed to ethynodiol diacetate (VI)[3] and ethindrone acetate (V, R = CH_3CO),[4] both containing a 17β-acetoxy function, it was decided to prepare the ester analog of I (R = H).

The process used for the preparation of I (R = H) (see Scheme I) was considered to be adaptable for the preparation of I (R = CH_3CO). However, neither 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol (III, R = H) nor 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one (IV, R = H) were found to be useful substrates for acetylation. Although the 17β-tertiary hydroxy was relatively easily esterifiable by hot acetic anhydride[5] or by acetic anhydride with acid catalysis,[6] the reactive 3-keto-$\Delta^{5(10)}$ system in IV (R = H), essential for the hydroperoxidation, and the diene system in III (R = H) underwent unwanted isomerization.[7]

Accordingly, we chose to investigate alternate procedures in the sequence for the formation of the 17β-acetoxy,17α-ethinyl moiety.

The formation of this moiety during the ethinylation reaction of the ketone II appeared possible since an oxyanion may be considered to be a generated species and might be available for rapid acylation.



Various solvent systems are known for carrying out the ethinylation of ketones; these include liquid ammonia and *t*-butyl alcohol. We considered that a preferred solvent system would be one wherein the availability of protons was low or nonexistent so that the solvent would react at a slow rate, if at all, with the esterification reagent and discharge at a slow rate, if at all, the oxyanion of "A." Dimethylformamide was considered to be such a solvent.[8]

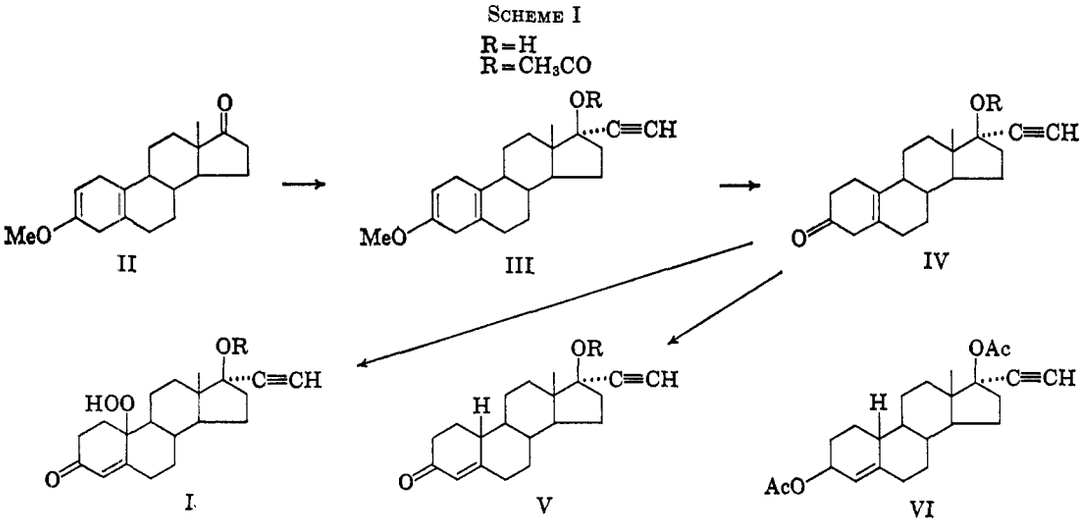
Accordingly, II was treated with sodium acetylide[9] in dimethylformamide at room temperature. After 15 min, acetic anhydride was added to the reaction medium. After an additional minute, isolation of the reaction product afforded an excellent yield of 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol 17-acetate (III, R = CH_3CO). This concomitant esterification could also be accomplished with tetrahydrofuran as the solvent.[10] In our opinion, this method constitutes a facile procedure for the esterification of the important steroid hormone class which bears the 17β-OH-17α-alkinyl grouping.

Proof of structure of III (R = CH_3CO) was effected by conversion of III (R = CH_3CO) with oxalic acid into 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one 17-acetate (IV, R = CH_3CO) which then, with hydrochloric acid, was converted into the known 17α-ethinyl-17β-hydroxy-4-estren-3-one 17-acetate (V, R = CH_3CO).[11]

In view of the ready esterification *via* the presumed species "A," it was felt that this same species could also be made available for esterification by base treatment of III (R = H). However, when III (R = H) was treated with potassium *t*-butoxide in dimethylformamide and then with acetic anhydride, the ethinyl

(1) (a) E. L. Shapiro, T. Legatt, and E. P. Oliveto, *Tetrahedron Lett.*, 663 (1964); (b) U. S. Patent 3,280,157 (Oct 18, 1966).
(2) (a) A. S. Watnick, J. Gibson, M. Vinegra, and S. Tolksdorf, *J. Endocrinol.*, **33**, 241 (1965); (b) A. S. Watnick, S. Tolksdorf, J. Kosierowski, and I. A. Tabachnick, Excerpta Medica International Congress Series No. III, IInd International Congress on Hormonal Steroids, Milan, May 23–28, 1966, Paper No. 123.
(3) G. Pincus, C. R. Garcia, M. Paniagua, and J. Shepard, *Science*, **138**, 439 (1962).
(4) E. Meers, *Intern. J. Fertility*, **9**, 1 (1964); H. C. Walser, R. R. Margulis, and J. E. Ladd, *ibid.*, **9**, 189 (1964).
(5) (a) L. Ruzicka and K. Hofmann, *Helv. Chim. Acta*, **20**, 1280 (1937); (b) C. W. Shoppee and D. A. Prins, *ibid.*, **26**, 185 (1943). In these references the configuration of the hydroxy function is β.
(6) I. Iriate, C. Djerassi, and H. J. Ringold, *J. Amer. Chem. Soc.*, **81**, 436 (1959).
(7) The formation of III (R = CH_3CO) from III (R = H) using acetic anhydride and pyridine is reported in British Patent 922,877 (April 3, 1963), although no physical constants are noted. In our hands the procedure was unsatisfactory because of substantial loss of the diene system in ring A.
(8) C. Burgess, D. Bunn, P. Feather, M. Howarth, and V. Petrow [*Tetrahedron*, **22**, 2829 (1966)] report etherification with methyl iodide in a sodamide–liquid ammonia medium.
(9) J. A. Campbell, J. C. Babcock, and J. A. Hogg, *J. Amer. Chem. Soc.*, **80**, 4717 (1958).
(10) We wish to thank R. Grocela and N. Murrill of the Process Research Development Department for carrying out this experiment.
(11) Compare ref 6, wherein V (R = CH_3CO) was prepared from V-(R = H) by acid esterification to 17α-ethinyl-3,5-estradiene-3,17-diol 3,17-diacetate followed by acid hydrolysis.

SCHEME I



moiety present in III (R = H) was extruded, and an excellent yield of the 17-ketone II was obtained.[12]

The β,γ-unsaturated ketone IV (R = CH_3CO), which had been obtained by oxalic acid hydrolysis of the 17-acetate III (R = CH_3CO), was converted by oxygenation into 17α-ethinyl-17β-hydroxy-10β-hydroperoxy-4-estren-3-one 17-acetate (I, R = CH_3CO), and thus our principal objective was attained.

Experimental Section[13]

3-Methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol 17-Acetate (III, R = CH_3CO). A.—3-Methoxy-2,5(10)-estradien-17-one (II) (40 g) was dissolved in 800 ml of dimethylformamide and stirred under an argon atmosphere. To the reaction mixture was added 13.41 g of sodium acetylide (2 equiv; 74.5 ml of 18% sodium acetylide[14] in xylene from which the xylene was partially removed by centrifugation), and the reaction was stirred at room temperature, under argon, for 15 min. With rapid agitation, 19.78 ml of acetic anhydride (1.5 equiv) was added and stirred for 1 min. The reaction mixture was poured into 8 l. of water containing 240 g of sodium chloride, and the resulting mixture was rapidly agitated for 2 hr; the precipitate was then separated by filtration and air dried to yield a solid which consisted essentially of III (R = CH_3CO) as measured by tlc (silica gel, chloroform–benzene 3:1). Crystallization from methanol–water containing a trace of pyridine yielded 21 g of a yellow solid, mp 160–165°. Recrystallization from methanol–water–pyridine afforded the analytical sample: mp 167–170°; $[\alpha]D$ +58°; nmr, δ (ppm) (TMS = 0) 0.85 ($C_{13}CH_3$), 1.98 ($C_{17}OCOCH_3$), 3.48 (C_3OCH_3 plus CH_3OH), 3.71 (C≡CH), 4.68 (C_2H); λ_{max} 3.08, 5.74, 5.90, 6.01, 7.94, and 8.20 μ; λ_{max} end absorption only; $\lambda_{max}^{aqueous\ HCl-MeOH}$ 239 mμ (ϵ 16,600).

Anal. Calcd for $C_{23}H_{30}O_3 \cdot {}^1/_4CH_3OH$: C, 77.03; H, 8.62. Found: C, 77.23, 76.91; H, 8.48, 8.36.

B.—To a solution of 20 g of II in 200 ml of tetrahydrofuran was added 200 ml of a suspension of 18% sodium acetylide in xylene. The reaction mixture was agitated at 25° for 4 hr. An aliquot of 12 ml (approximately 600 mg of steroid) was then removed, mixed with 1.6 ml of acetic anhydride, and stirred at room temperature for 15 min. After pouring into ice water and extracting with methylene chloride, there was obtained 700 mg of crude product, the major component exhibiting the same migration rate as III (R = CH_3CO) by tlc (silica gel, hexane–acetone 7:3). Crystallization from aqueous methanol (with trace of pyridine) gave III (R = CH_3CO), comparison with product from A by infrared and nmr spectra and tlc.

17α-Ethinyl-17β-hydroxy-5(10)-estren-3-one 17-Acetate (IV, R = CH_3CO).—To a suspension of 19 g of 3-methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol 17-acetate (III, R = CH_3CO) in 1625 ml of methanol and 325 ml of water was added 19 g of oxalic acid. The reaction mixture was stirred at room temperature for 1.75 hr (solution occurring at 1.25 hr) and then poured into 16 l. of water. The insolubles were collected by filtration, washed with water, and dried in air at 30° to yield 15 g of solid which was principally one component as measured by tlc (silica gel, $CHCl_3$). This solid exhibited no absorption in the ultraviolet from 220–350 mμ at approximately 0.0025% concentration, the significant infrared absorption bands being λ_{max} 3.04, 5.72, 5.82, 8.02, and 8.15 μ. This solid was used in the next step because attempted purification by crystallization or silica gel column chromatography was unsuccessful.

17α-Ethinyl-17β-hydroxy-4-estren-3-one 17-Acetate (V, R = CH_3CO). A. From 17α-Ethinyl-17β-hydroxy-5(10)-estren-3-one (IV, R = H).—A solution consisting of 1 g of 17α-ethinyl-17β-hydroxy-5(10)-estren-17β-ol-3-one (IV, R = H), 1.25 ml of concentrated hydrochloric acid, 180 ml of methanol, and 20 ml of water was refluxed for 0.5 hr. The reaction mixture was then diluted with 1.5 l. of water to give a precipitate which was collected by filtration and dried. This solid of V (R = H) was dissolved in 3 ml of glacial acetic acid and 1 ml of trifluoroacetic anhydride, and allowed to stand at room temperature for 0.5 hr. The reaction mixture was poured into 50 ml of water, filtered, and twice crystallized from acetone–hexane to yield 17α-ethinyl-17β-hydroxy-4-estren-3-one 17-acetate (V, R = CH_3CO): mp 161–163°; $[\alpha]D$ ($CHCl_3$) −30.3°; λ_{max} 239 mμ (ϵ 16,900) [lit.[11] mp 161–162°; $[\alpha]D$ ($CHCl_3$) −33°; $\lambda_{max}^{95\%\ EtOH}$ 240 mμ (log ϵ 4.20)]; λ_{max} 3.08, 4.72, 5.72, 6.01, 6.19, 8.01, 8.10, 8.20, and 11.22 μ.

B. From 17α-Ethinyl-17β-hydroxy-5(10)-estren-3-one 17-Acetate (IV, R = CH_3CO).—A mixture of 1 g of 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one 17-acetate (IV, R = CH_3CO), 1.25 ml of concentrated hydrochloric acid, 180 ml of methanol and 20 ml of water was brought to reflux and allowed to cool to room temperature over a 2.5-hr period. The reaction mixture was poured into 1.5 l. of water, and the resulting solid collected by filtration, dried, and twice crystallized from isopropyl ether to yield V (R = CH_3CO): mp 157–161° [mixture melting point with V (R = CH_3CO) from A 157–161°]; $[\alpha]D$ (CH_3Cl_3) −26.8°; λ_{max} 239 mμ (ϵ 16,300); infrared identical with V (R = CH_3CO) from A.

10β-Hydroperoxy-17α-ethinyl-17β-hydroxy-4-estren-3-one 17-Acetate (I, R = CH_3CO).—Oxygen was slowly bubbled through a solution of 2 g of 17α-ethinyl-17β-hydroxy-5(10)-estren-3-one 17-acetate (IV, R = CH_3CO) in a mixture of 36 ml of carbon tetrachloride and 18 ml of hexane while irradiating with fluorescent light. At 18 hr a yellow oily solid was removed and the oxygenation continued. At 90 hr a white solid (640 mg, 1 spot tlc, silica gel, 3:1 $CHCl_3$–EtOAc) was collected and crystallized from methanol–water to yield 10β-hydroperoxy-17α-ethinyl-17β-hydroxy-4-estren-3-one 17-acetate (I, R = CH_3CO): posi-

(12) De-ethination to the 17-ketone has been effected (a) with boiling aqueous alkali by H. Langecker [*Naturwissenschaften*, **46**, 601 (1959)] and (b) with potassium *t*-butoxide in *t*-butyl alcohol as cited by H. Ringold in "Mechanism of Action of Steroid Hormones," C. A. Villee and L. L. Engle, Ed., Pergamon Press Inc., New York, N. Y., 1961, p 218.

(13) Melting points were determined on a Kofler block and are uncorrected. Nmr spectra were measured with a Varian A-60A spectrometer. Rotations are in dioxane at 25° at about 1% concentration; infrared spectra are from the solids in Nujol, and ultraviolet spectra are of methanol solutions unless otherwise stated.

(14) Air Reduction Company, Inc., Middlesex, N. J.

tive starch iodide test; mp 178–181°, bubbling; $[\alpha]D$ −29°; λ_{max} 233 mμ (ε 15,000); λ_{max} 3.02, 3.05, 5.69, 5.98 (shoulder), 6.02, 6.07 (shoulder), 7.95, and 8.08 μ; nmr, δ (ppm) (TMS = 0): 0.85 ($C_{13}CH_3$), 1.98 ($C_{17}OCOCH_3$), 3.47 (C≡CH), 5.88 (C_4H), 11.28 (C_{10}-O-OH).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 71.11; H, 7.45.

Generation of 3-Methoxy-2,5(10)-estradien-17-one (II) from 3-Methoxy-17α-ethinyl-2,5(10)-estradien-17β-ol (III, R = H).—To a solution consisting of 0.2 g of III (R = H) in 10 ml of dimethylformamide under nitrogen was added 0.1 g of potassium *t*-butoxide. After 5 min at room temperature, 0.11 ml of acetic anhydride was added. One minute later the reaction mixture was poured into 200 ml of water. The pH was adjusted to about 3 with dilute HCl, and the insolubles, which were collected by filtration and dried at 60° under vacuum, weighed 140 mg. The infrared spectrum matched that of authentic II.

Registry No.—I (R = CH_3CO), 13236-11-8; III (R = CH_3CO), 13251-69-9; V (R = CH_3CO), 51-98-9.

Acknowledgment.—We wish to thank Mr. Milton Yudis and Mrs. Henrietta Marigliano for their aid in the nmr interpretations.

Organocadmium Reagents. V. Reaction with α-Halo Esters and Ketones[1a,b]

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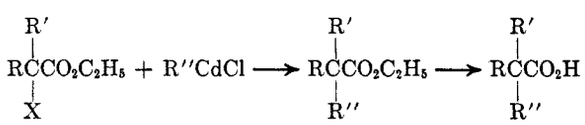
In view of the diminished reactivity of organocadmium compounds as compared to lithium or magnesium reagents,[2] it is attractive to consider new syntheses of compounds containing functional groups which would not survive treatment with the more reactive organometallic reagents. Since organocadmium reagents are known to displace halogens in a few instances[3] but do not appear to decompose esters,[2,4] we undertook an investigation of the behavior of some α-halogenated esters with these reagents. If displacement of halogen were to occur in preference to reaction at the ester site, the reaction would be potentially useful as a synthetic route to more complex acids and derivatives.



R, R′ = H, CH_3, $CO_2C_2H_5$
R″ = C_6H_5, α-$C_{10}H_7$

This hypothesis was borne out by experiment to a limited extent. We found the reaction to be sensitive to the structure of the halo ester, solvent, and temperature, as can be seen from the results summarized in Table I. The bromo esters of acetic and propionic acids could be converted, respectively, into arylacetic and α-arylpropionic acids in yields of 40–62% under certain experimental conditions. Bromoisobutyrate did not form displacement product in ether or THF but was recovered partially or completely. We found no trace of a Claisen product, ethyl 2,2,4-trimethyl-3-oxopentanoate, as reported by Cason and Fessenden[5] from a similar reaction with the *n*-butylcadmium reagent in benzene.

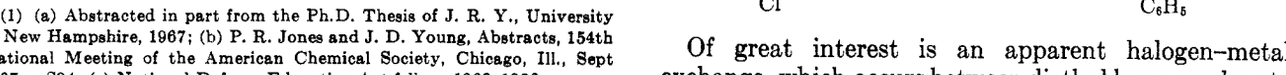
From the two chloro esters examined, only starting material, solvolysis product, or dehalogenative coupling products could be isolated.

The striking effect of solvent on the displacement was unexpected. Thus the conversion of bromoacetate into arylacetic acid was four to five times greater in THF than in ether. Under similar reaction conditions bromopropionate reacted efficiently in ether but failed completely in THF.

Optimum temperature for reactions in THF appears to depend on the cadmium reagent. Highest conversions with the phenylcadmium reagent in THF were realized at ice-bath temperature, while the α-naphthylcadmium reagent was considerably more reactive at room temperature. At least two factors may account reasonably for this temperature effect: increased coupling of phenyl reagent at the higher temperature and lower reactivity of the α-naphthylcadmium reagent, as well as its observed precipitation in THF at ice-bath temperature. By-products from the two cadmium reagents were biphenyl and naphthalene in every case, although the amounts of these hydrocarbons were not usually determined.

The reaction with α-halo ketones proceeded similarly, but the yields were generally lower than those from esters. Deoxybenzoin could be isolated only in 3–31% yield from phenacyl bromide and phenylcadmium reagent, along with the coupling products, biphenyl and 1,2-dibenzoylethane.

To our knowledge, a displacement of halogen in simple α-halo esters has not been reported up until now. Although Gross and Freiberg[4] recently effected the displacement of the chloro group in methyl chloromethoxyacetate, this substrate is both an ether and an ester; and the replacement of halogen in α-halo ethers by organocadmium reagents is well known.[3a,3b]



Of great interest is an apparent halogen–metal exchange, which occurs between diethyl bromomalonate and the phenylcadmium reagent. Both malonic ester and bromobenzene were isolated in equal amounts, roughly 75% yield. Thus the displacement method is not applicable to the synthesis of substituted malonic acids.

A similar halogen–metal exchange reaction was proposed earlier to explain Reformatsky and Claisen products from organocadmium reagents.[5]

(1) (a) Abstracted in part from the Ph.D. Thesis of J. R. Y., University of New Hampshire, 1967; (b) P. R. Jones and J. D. Young, Abstracts, 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967, p S94; (c) National Defense Education Act fellow, 1963–1966.

(2) J. Cason, *Chem. Rev.*, **40**, 15 (1947); D. A. Shirley, *Org. Reactions*, **8**, 27 (1943).

(3) (a) R. K. Summerbell and L. N. Bauer, *J. Amer. Chem. Soc.*, **58**, 759 (1936); (b) C. D. Hurd and R. P. Holysz, *ibid.*, **72**, 2005 (1950); (c) R. C. Fuson, S. B. Speck, and W. R. Hatchard, *J. Org. Chem.*, **10**, 55 (1945); (d) P. Chancel, *Bull. Soc. Chim. Fr.*, 228 (1951); (e) D. V. Nightingale, W. S. Wagner, and R. H. Wise, *J. Amer. Chem. Soc.*, **75**, 4701 (1953); (f) P. R. Jones and A. A. Lavigne, *J. Org. Chem.*, **25**, 2020 (1960); (g) F. N. Jones and C. R. Hauser, *ibid.*, **27**, 3364 (1962); (h) P. R. Jones, R. G. Nadeau, and G. A. Crosby, Abstracts A of IUPAC Congress, London, 1963, p 267; (i) P. R. Jones, C. J. Jarboe, and R. Nadeau, *J. Organometal. Chem.*, **8**, 361 (1967).

(4) H. Gross and J. Freiberg, *Chem. Ber.*, **99**, 3260 (1966).

(5) J. Cason and R. J. Fessenden, *J. Org. Chem.*, **22**, 1326 (1957).