violet spectrum λ_{max}^{MeOH} 241.5 mμ (log ε 4.67), 278 (3.70), 325–329 (3.52), and 337 (3.60). *Anal.* Calcd. for $C_{20}H_{23}ClNO_4 \cdot H_2O$: C, 60.86; H, 6.33; N, 3.55. Found: C, 60.26; H, 6.39; N, 3.33.

1-(4'-Methoxybenzyl)-5,6,7-trimethoxyisoquinoline Methiodide (VI).—A solution of 130 mg. of the isoquinoline free base XVII in 4 ml. of methanol was refluxed with methyl iodide (2 ml.) on a water bath for 2.5 hr. under nitrogen. The solvent and excess methyl iodide were evaporated under nitrogen to a yellow residue which was crystallized from methanol to yield yellow plates, m.p. 181–182°, ultraviolet spectrum λ_{max}^{MeOH} 265 mμ (log ε 4.61) and 318 mμ (log ε 3.69). *Anal.* Calcd. for $C_{21}H_{24}INO_4$: C, 52.39; H, 4.99; N, 2.91. Found: C, 52.41; H, 5.26; N, 2.77. The infrared (KBr) and n.m.r. spectra (see Figure 3) were identical with those of an authentic sample of takatonine iodide. The melting point was not depressed upon admixture with the authentic sample of takatonine iodide.

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Stereochemistry of Enolization of 17-Keto Steroids

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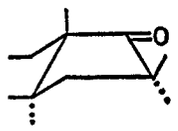
In the enolization of 17-keto steroids the 16α-proton is preferentially removed. Similarly, the protonation of the corresponding enol proceeds preferentially from the α side. This preference is due to steric reasons only.

The influence of steric factors on the course of the enolization–ketonization reaction has been well documented.[1] With cyclic ketones of fixed conformation such as steroid ketones an additional and often overriding factor is stereoelectronic control.[2] Owing to the best orbital overlap in the transition state there is a preference for the removal or addition of the axial proton on the α-carbon in the rate-determining step. In most cases of steroid ketones the steric and stereoelectronic effect are in conflict[2,3] and it is not possible to assess the contribution of each toward the stereochemical course of enolization and ketonization. The C-17 ketone is unique in this respect, since enolization may be expected to be affected by steric factors alone. It has been adequately demonstrated[4,5] that the angle between the plane of the 17-carbonyl and either of the 16α or 16β bonds is identical and hence that ring D in 17-keto steroids is the envelope conformation (A).[5]



A

Since both C-16 bonds have the same degree of axial or equatorial character,[6] no stereoelectronic effect in the enolization of the 17-ketone should exist and preferential removal of either the 16α- or 16β-proton must depend on steric effects alone. The nature and extent of these factors is of additional interest because 17-keto steroid hormones frequently participate in biotransformations which involve reactions of the α- or β-protons of C-16.

The recent successful stereoselective introduction of deuterium into the 16α- and 16β-positions[7] provided the means for preparation of suitable substrates for enolization studies. The use of a hydrogen isotope in this work avoids the obvious objections that may be directed to other C-16 substituents differing greatly from hydrogen in size and electronic character. The stereoselectively 16α- and 16β-tritiated estrone benzoates were prepared by the sequences used in the preparation of the corresponding deuterio compounds[7] in which the orientation of the isotope was confirmed by nmr spectroscopy. Reduction of 16α,17α-epoxyestra-1,3,5(10)-trien-3-ol (I) with lithium aluminum hydride-^3H gave 16β-tritio-17α-estradiol (IIa), which was benzoylated at C-3 and oxidized with the Jones reagent[8] to give the 16β-tritioestrone benzoate (IIIa) (Chart I). The undiminished specific activity of IIIa indicated that the oxidation proceeded without enolization and hence without epimerization. Tritium was introduced into the 16α-position by lithium aluminum hydride reduction of estrone enol diacetate[9] and decomposition of the complex with tritiated acetic acid. The 16α-tritio-17β-estradiol (IVa) thus obtained was benzoylated to IVb and oxidized, also without significant change in specific activity, to 16α-tritioestrone benzoate (IIIb). Based on the deuterium experiments, the stereoselectivity of the tritium introduction was at least 80%, while biochemical evidence[10] supports better than 90% stereoselectivity. The location of the tritium was solely at C-16, since all radioactivity was lost in each instance by exchange in aqueous alkali.

The two epimeric tritiated derivatives IIIa and IIIb were diluted to the same specific activity with inert material and were subjected to acid-catalyzed enolizing

(1) (a) H. E. Zimmerman, *J. Org. Chem.*, **20**, 549 (1955); H. E. Zimmerman and T. W. Cutshall, *J. Am. Chem. Soc.*, **81**, 4305 (1959), and preceeding papers; O. H. Wheeler and J. L. Mateos, *J. Org. Chem.*, **22**, 605 (1957); (b) for a brief review of the topic, see H. E. Zimmerman in "Molecular Rearrangements," part I, P. DeMayo, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, pp 362–372.

(2) E. J. Corey and R. A. Sneen, *J. Am. Chem. Soc.*, **78**, 6271 (1956); S. K. Malhotra and H. J. Ringold, *ibid.*, **86**, 1997 (1965).

(3) R. Villotti, H. J. Ringold, and C. Djerassi, *ibid.*, **82**, 5693 (1960); R. Mauli, H. J. Ringold, and C. Djerassi, *ibid.*, **82**, 5494 (1960); C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *ibid.*, **82**, 5488 (1960).

(4) (a) J. Fajkos, *J. Chem. Soc.*, 3966 (1959); (b) J. Fishman and C. Djerassi, *Experientia*, **16**, 138 (1960); (c) J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, **23**, 1190 (1958).

(5) F. V. Brutcher and W. Bauer, *J. Am. Chem. Soc.*, **24**, 2236 (1962).

(6) The term bisectional has been applied to these bonds.[5]

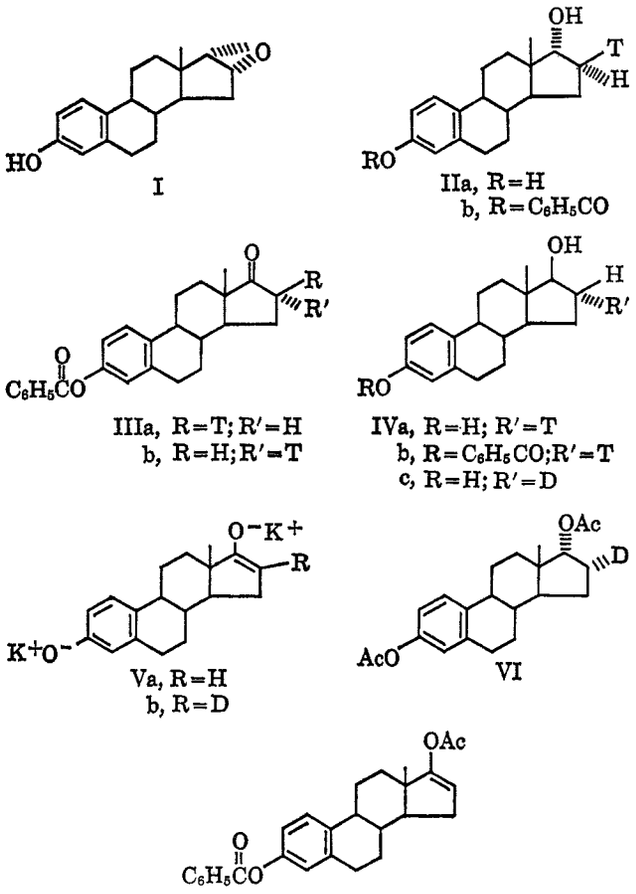
(7) J. Fishman, *J. Am. Chem. Soc.*, **87**, 3455 (1965).

(8) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

(9) W. G. Dauben and J. F. Eastham, *J. Am. Chem. Soc.*, **75**, 1718 (1953).

(10) J. Fishman, to be published.

CHART I



conditions in an aqueous organic solvent. Aliquots were removed at specified intervals, diluted with distilled water, and frozen immediately, and a portion of the water was freeze distilled. The tritium content of each distillate was measured in a liquid scintillation counter, using suitable quenching corrections for any codistilled organic solvent. The results obtained under several conditions are reported in Tables I–III.

Two considerations deserve emphasis. First, enolization of the tritium-labeled ketone will be subject to a substantial isotope effect.[11] In a low specific activity substrate, the isotope effect will serve to select preferentially the unlabeled molecules for enolization. It may be expected, however, that the primary and secondary isotope effects will *not* show steric discrimination, will be identical in both compounds IIIa and IIIb, and therefore will not influence the *difference* between the epimers.

TABLE I[a]

Time, hr	Counts/min in distillate: 16α-³H (IIIb)	16β-³H (IIIa)	16α/16β
1	460	110	4.2
2	860	200	4.3
3	1,360	350	3.9
5	1,960	420	4.5
24	4,200	1,010	4.2
120	28,700	13,630	2.1

[a] 2.0 mg each of IIIa and IIIb (130,000 counts/min/mg) in 8.8 ml of acetic acid, 1 ml of water, and 0.2 ml of H_2SO_4, at 38°.

TABLE II[a]

Time, hr	Counts/min in distillate: 16α-³H (IIIb)	16β-³H (IIIa)	16α/16β
2	280	43	6.5
4	905	145	6.2
8	1770	280	6.1

[a] 1 mg each of IIIa and IIIb (130,000 counts/min/mg) in 5 ml of dioxane and 5 ml of 4 *N* H_2SO_4.

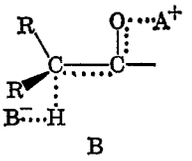
TABLE III[a]

Time, hr	Counts/min in distillate: 16α-³H (IIIb)	16β-³H (IIIa)	16α/16β
4	1500	81	18
5	2240	152	15
24	6708	364	18

[a] 1.5 mg each of IIIa and IIIb (130,000 counts/min/mg) in 5 ml of ethanol, 4.2 ml of water, and 0.8 ml of 70% $HClO_4$.

The second point which merits consideration is that, although the enolizations were studied under reversible conditions, circumstances exist that the validity of the results obtained is unaffected. This is so because, in the low specific activity substrate, the protonation of an enol obtained by the abstraction of a 16-tritium atom will produce an unlabeled ketone molecule which does not further affect the results. In the case of a 16-tritioenol produced by 16α-proton abstraction from IIIa, the stereochemistry of ketonization being akin to that of enolization will tend to regenerate the starting material. The 16-tritioenol species obtained by the 16β-proton abstraction from IIIb will, of course, by the same criterion be epimerized on protonation to IIIa, but owing to the initial stereochemical enolization effect this reaction will constitute only a minor portion of the interconversions occurring in the time studied. All these factors are emphasized under the relatively slow enolizing conditions used. That this situation exists is evident from the constancy of the 16α/16β differential over long periods of time in Tables I–III, which could not be true if substantial epimerization had occurred. Only after 5 days is a change in the ratio observed, indicating that considerable epimerization had occurred.

The results listed in Tables I–III show a 4- to 18-fold preference for the removal of the 16α-proton in the acid-catalyzed enolization of the 17-ketone. It is clear, therefore, that a substantial steric hindrance to the removal of the 16β-proton exists. From consideration of the geometry of ring D and the geometry of the enolization transition state, these results could very well be anticipated. The termolecular transition state suggested by Swain[12] (B) has been supported by



B

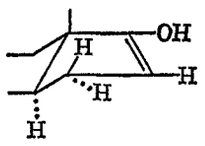
recent evidence.[13] In acid-catalyzed enolization, the geometry of the transition state approaches that of the enol,[14] with the α-carbon sp^2 hybridized. Inspection of the Dreiding model of the 17-enol, in the envelope conformation (C), shows clearly that the 16β side is

(11) C. G. Swain, E. C. Stivers, J. F. Renwer, and L. J. Schaad, *J. Am. Chem. Soc.*, **80**, 5885 (1958).

(12) C. G. Swain, *ibid.*, **72**, 4578 (1950).

(13) W. D. Emmons and M. F. Hawthorne, *ibid.*, **78**, 5593 (1956).

(14) G. S. Hammond, *ibid.*, **77**, 334 (1955).



C

effectively shielded by the C-18 methyl group and the pseudo-axial 15β-hydrogen, while the 16α side has only to contend with the effect of the axial 14α-hydrogen and the pseudo-equatorial 15α-proton. It is not surprising, therefore, that approach of the proton-abstracting base to C-16 occurs from the α side.

The extent of the steric effect may be expected to depend on a number of factors other than the size of the proton-abstracting nucleophiles. These include the electronegativity of the nucleophile and the acidity of the catalyst which affects the geometry of the transition state.[1,2,11,13,15] Hence, it is not surprising to find differences in the relative amount of isotope removed from the two substrates under several conditions.

The nature of the steric effect observed was further confirmed by preparing the enol diacetate from both IIIa and IIIb under the exact conditions of exchange with isopropenyl acetate in the presence of a catalytic amount of sulfuric acid. The product VII obtained from each reaction was recrystallized to constant specific activity. In accordance with expectation, the enol diacetate derived from IIIa lost only 22% of the tritium present in the starting material, while that obtained from IIIb suffered a 82% loss, a ratio of 3.7 in favor of removal of the 16α-proton. It may be added that in this case the products were obtained under what may be considered essentially irreversible conditions, since the enol is trapped as the acetate.

It has been suggested[13] that base-catalyzed enolization is more affected by steric factors. The 16β- and 16α-labeled compounds IIIa and IIIb were subjected to base-catalyzed enolization in two different systems. In the presence of sodium acetate in acetic acid, enolization was either so slow or the isotope effect was so large[16] that the tritium in the distillate was insufficient for accurate comparison within a reasonable time. On the other hand, in the presence of aqueous sodium hydroxide enolization was so rapid that epimerization occurred and no important differences could be observed.

The enolization–ketonization reactions are in micro-equilibrium[1b] and the transition states for each are essentially identical. Therefore, the stereochemistry of ketonization must be intimately related to the stereochemistry of enolization, and the ketonization of the enol of the 17-ketone must therefore also proceed preferentially from the α side. There is adequate evidence that almost all reactions involving ketonization of the C-17 enol initially yield the 16α-substituted compounds.[17] However, these reactions involve atoms other than hydrogen, and it was of interest to study the ketonization of the enol with hydrogen or its isotope. The potassium enolate of estrone Va prepared with potassium triphenylmethane,[18] was quenched with deuterioacetic acid in D_2O. The deuterioestrone was isolated and reduced with $LiAlH_4$, and the deuterated estradiol IVc obtained was converted to the diacetate. It has been shown[7] that 16β- and 16α-deuterioestradiols-17β can be distinguished from their $H_{17,16}$ coupling constant, which is 9 cps for the former and 6.5 cps for the latter. Nmr analysis of the acetate of IVc showed it to be at least 80% 16α-deuterioestradiol diacetate. The composition of this estradiol mixture could be more accurately observed when the 17β-acetoxy group was epimerized to the 17α-acetoxy compound VI by the procedure of Henbest.[19] In this series the difference between the $H_{16,17}$ coupling constant for the 16α- (6.5 cps) and 16β- (0.3 cps) deuterio derivatives is more easily observed. In the center of the H_{17} doublet at 288 cps a small singlet integrating to about 15% was present, showing the presence of that amount of 16β-deuterioestradiol. To confirm these results, the potassium 16-deuterio enolate Vb was prepared from 16,16-dideuterioestrone.[7] This was quenched with dilute acetic acid and the estrone obtained was reduced to estradiol-17β. Nmr analysis of the diacetate of this product showed it to consist of at least 80% of the 16β-deuterio derivative. From these results it is apparent that ketonization of the 17-enol with deuterium or hydrogen occurred preferentially from the α side by a factor of about 5, in substantial agreement with the enolization results.

It is important to emphasize that the steric preferences here detailed do not necessarily reflect the thermodynamic stability of 16-substituted ketones. The enolization and ketonization reactions in the transition state require approach of the nucleophile or electrophile perpendicular to the incipient double bond and hence almost parallel to the C-18 methyl group. In contrast, the 16β substituent on the tetrahedral C-16 carbon in 17-keto steroids is deflected from that plane by about 35°, relieving the steric interaction substantially. Therefore, the stability of 16α- *vs.* 16β-substituted compounds will vary with nature of the substituent at C-16.[20] These results, however, can help to rationalize some aspects of the chemistry of ring-D 16,17-ketols, since the more rapid enolization of the 16α-proton may account for the much greater ease of the irreversible rearrangement of 16β-hydroxyestrone as compared with 16α-hydroxyestrone.[21] It is also perhaps of significance that most of the biochemical reactions of 17-keto steroid hormones at C-16 occur primarily from the α side, and the implications of the current work in the biochemistry of steroids are now being investigated.

Experimental Section[22]

16β-Tritio-17α-estradiol Benzoate (IIb).—A solution of 20 mg of 16α,17α-epoxyestra-1,3,5-trien-3-ol (I) in 5 ml of tetrahydro-

(15) H. Shechter, M. J. Collins, R. Dessy, Y. Okuzumi, and A. Chen, *J. Am. Chem. Soc.*, **84**, 2905 (1962).

(16) J. R. Jones, *Trans. Faraday Soc.*, **61**, 95 (1965).

(17) *Inter alia*, J. Fajkos, *Chem. Listy*, **48**, 1800 (1954); M. N. Huffman and M. H. Lott, *J. Biol. Chem.*, **213**, 343 (1955).

(18) H. O. House and V. Kramer, *J. Org. Chem.*, **27**, 4146 (1962).

(19) H. B. Henbest and W. R. Jackson, *J. Chem. Soc.*, 954 (1962).

(20) J. Fajkos and F. Sorm, *Collection Czech. Chem. Commun.*, **19**, 349, 766 (1954); **20**, 1464 (1955); *Chem. Listy*, **50**, 791 (1956).

(21) W. S. Johnson, B. Gastambide, and R. Pappo, *J. Am. Chem. Soc.*, **79**, 1991 (1957); J. Fishman, *ibid.*, **82**, 6143 (1960).

(22) Nmr spectra were determined in carbon tetrachloride on a Varian A-60 instrument, using tetramethylsilane as an internal standard. Chemical shifts are recorded in cycles per second downfield from tetramethylsilane at 0 cps. The tritium counts were obtained on a Packard Tri-Carb liquid scintillation counter using scintillant mixtures previously described: R. J. Herberg, *Anal. Chem.*, **32**, 42 (1960).

furan was refluxed with 5 mg of lithium aluminum hydride-^{3}H (1.0 mcurie) for 2 hr. The reaction mixture was decomposed with dilute sulfuric acid, and the aqueous mixture was extracted with chloroform, which was washed with dilute sulfuric acid solution and then with 5% sodium bicarbonate solution, dried, and evaporated. The residue was taken up in 0.1 *N* NaOH solution (5 ml) and treated with 0.2 ml of benzoyl chloride. After shaking at room temperature for 10 min, the flocculent precipitate was filtered off and washed well with dilute sodium carbonate solution and water. After air drying, the precipitate was submitted to preparative thin layer chromatography on silica gel in the system ethyl acetate–cyclohexane (70:30). The zone corresponding to 17α-estradiol 3-benzoate was eluted with chloroform. The 16β-tritio-17α-estradiol 3-benzoate (IIb) thus obtained weighed 8.6 mg and was diluted with 43 mg of inert material, and recrystallized from acetone–petroleum ether to a constant specific activity of 3.10×10^6 counts/min/mg.

16β-Tritioestrone Benzoate (IIIa).—A 31-mg sample of IIb (3.10×10^6 counts/min/mg) was dissolved in 5 ml of acetone and cooled in an ice bath and 2 drops of Jones reagent[8] were added with shaking. After 10 min at 0°, the mixture was poured into ether, which was washed with water and cold sodium bicarbonate solution. After drying and evaporation the residue was recrystallized twice from acetone–petroleum ether (bp 30–60°) to give 16β-tritioestrone benzoate (IIIa), mp 218–220°, 3.10×10^6 counts/min/mg. Further crystallization did not alter the specific activity significantly. A sample of IIIa was warmed with 0.5 *N* sodium hydroxide for 2 hr. The estrone recovered after acidification exhibited a specific activity of 180 counts/min/mg, which decreased to 40 counts/min/mg on further recrystallization from ethanol.

16α-Tritio-17β-estradiol 3-Benzoate (IVb).—A suspension of 10 mg of $LiAlH_4$ in 10 ml of purified tetrahydrofuran was cooled to 0°, and a solution of 20 mg of estrone enol diacetate in 5 ml of tetrahydrofuran was added with stirring. After stirring at 0° for 1 hr, 1 ml of acetic acid-^{3}H (prepared from 1 ml of acetic anhydride and 0.5 mcurie of tritiated water) was added dropwise. The usual work-up yielded a mixture which was benzoylated as described above. 16α-Tritio-17β-estradiol 3-benzoate (IVb), 3.4 mg, was obtained by preparative thin layer chromatography on silica in 7:3 ethyl acetate–cyclohexane. Dilution with 34 mg of inert material was followed by successive recrystallizations from acetone–petroleum ether to constant specific activity of 5.42×10^6 counts/min/mg.

16α-Tritioestrone Benzoate (IIIb).—A sample of IVb of the above specific activity was oxidized with Jones reagent as described. The product obtained was recrystallized from acetone–petroleum ether to give IIIb of constant specific activity of 5.24×10^6 counts/min/mg. A sample of IIIb on warming with 0.5 *N* NaOH gave estrone devoid of any significant radioactivity.

Acid-Catalyzed Enolization Studies.—The 16β- and 16α-tritiated estrone derivatives IIIa and IIIb were diluted with inert material to give products of similar specific activity (IIIa, 144,000 counts/min/mg; IIIb, 138,000 counts/min/mg). Equal weight samples of IIIa and IIIb of above specific activity were dissolved in 10 ml of the various enolizing media described in Tables I–III. Simultaneous experiments were performed on the 16α- and 16β-tritiated substrates; 1-ml aliquots were removed at intervals, diluted with 5 ml of distilled water, and immediately frozen in an acetone–Dry Ice bath. The frozen samples were then lyophilized under high vacuum, and 3.5 ml of distillate was collected in each case. Three 1-ml samples of the distillate were submitted for counting.

Base-Catalyzed Enolization Studies.—In the presence of sodium acetate in acetic acid after 24 hr only 4 counts/min (IIIb) and 0 counts/min (IIIa) were present in the distillate, and the experiment was not pursued further.

In 0.1 *N* NaOH in 50% ethanol after the first 5 min there was no further increase in the radioactivity of the distillate, which calculated out to complete exchange in each case.

Enol Acetylation of IIIa and IIIb.—A sample of 128 mg of IIIb (5100 counts/min/mg) was dissolved in 10 ml of isopropenyl acetate, and 0.5 ml of a catalyst solution prepared from 5 ml of isopropenyl acetate and 0.1 ml of sulfuric acid was added. The solution was distilled slowly for 1 hr, during which 3 ml of distillate was collected. Another 5 ml of isopropenyl acetate and 0.25 ml of catalyst solution was added, and the solution was distilled slowly for another 1.5 hr. It was then diluted with ether, washed with cold 5% $NaHCO_3$ solution, dried, and evaporated. The residue was chromatographed on acid-washed alumina, and 86 mg of 17 acetoxyestra-1,3,5(10),16-tetraen-3-ol benzoate (VII) was eluted with 1:1 petroleum ether–benzene. Recrystallization from acetone–petroleum ether gave VII of constant specific activity of 840 counts/min/mg which corresponds to IIIb with 930 counts/min/mg and represents a loss of 82% of the tritium.

The analytical sample of VII melted at 153–155°.

Anal. Calcd for $C_{27}H_{30}O_4$: C, 77.48; H, 7.23. Found: C, 77.35; H, 6.89.

Exactly the same procedure was carried out on a sample of the 16β-tritio derivative IIIa, of the same specific activity (5100 counts/min/mg). The enol acetate obtained exhibited constant specific activity of 3580 counts/min/mg, equivalent to 4000 counts/min/mg of starting material and representing a 22% loss of tritium.

Deuteration of Estrone Enolate.—To a solution of 4.7 g of triphenylmethane in 15 ml of freshly distilled dimethoxyethane was added 0.8 g of potassium in small pieces. The mixture was stirred overnight in a nitrogen atmosphere. To the deep red solution 2.2 g of estrone in 10 ml of dimethoxyethane was added dropwise with stirring. The resultant suspension which was still red was now added slowly to an ice-cooled, stirred solution of deuterioacetic acid (prepared from 8 ml of deuterium oxide and 3 ml of acetic anhydride). After stirring for 2 min, the mixture was diluted with ether, dried with $MgSO_4$, and filtered, and the filtrate was added slowly to a stirred suspension of $LiAlH_4$ in ether at 0°. After stirring for 1 hr at room temperature, the excess reagent was decomposed with wet ether and the organic layer was filtered and extracted with 5% NaOH solution. The alkaline extract was then acidified with dilute hydrochloric acid and the precipitated 17β-estradiol was filtered off, dried, and recrystallized from benzene to give 1.2 g of pure material. One portion of the deuterated estradiol was converted to the diacetate, the nmr spectrum of which exhibited a doublet at 278 cps (J = 6.5 cps.), indicating the deuterated product to be at least 80% 16α-deuterio-17β-estradiol (IVc)

Another portion of the deuterated estradiol-17β obtained above was dissolved in pyridine and treated with *p*-toluenesulfonyl chloride to yield, after the usual work-up, 300 mg of the 3,17-ditosylate derivative, which without further purification was dissolved in 21 ml of N-methylpyrrolidone. Tetrabutylammonium acetate (1.8 g) was then added, and the mixture was kept at 150–160° for 4 hr. The solution was diluted with water and extracted into ether which was evaporated, and the residue was hydrolyzed with 5% alcoholic KOH for 1 hr. After the usual work-up the 17α-estradiol was obtained pure by preparative thin layer chromatography on silica in 100% ethyl acetate. The diacetate VI was prepared; its nmr spectrum exhibited a doublet at 288 cps (J = 6.5 cps). At the center of the doublet a small singlet integrating to about 15% was present and could be assigned to 16β-deuterio-17α-estradiol.

Protonation of 16,16-Dideuterioestrone Enolate.—The above experiment was repeated except that the starting material was 16,16-dideuterioestrone and the potassium enolate Vb was quenched with dilute acetic acid. The deuterated estradiol-17β diacetate obtained after acetylation exhibited in the nmr spectrum a doublet at 277 cps (J = 9 cps), indicating it to be at least 85% 16β-deuterio-17β-estradiol diacetate.

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