butadiene,[9] 2,3-di-*t*-butylbutadiene[12]) all lack ^3J_s. However in other cases the use of ^3J_s can be powerful, as is shown by the difference between the values for butadiene[9] (10.41 c.p.s.) with a dihedral H–C–C–H angle of 180° and 1,3-cyclohexadiene[27] (5.14 c.p.s.) which has a dihedral angle probably within 20° of zero. The ratio of the two values is 2.0 compared to the ratio of 1.1 calculated by Karplus[7] for ethane and the observed ratio of 1.6 for ethylene.[24] The discrepancy may be indicative of the nonplanarity of cyclohexadiene.

These studies, including the data previously published in the literature,[31] have established the values of coupling constants to be expected for the *s-trans* conformation of butadiene derivatives and have indicated (and partly substantiated) the probable values for other conformations. The use of n.m.r. coupling constants has been shown to be a potentially powerful tool for determining the conformation of such molecules. Work is in hand with the aim of obtaining more definite values (including signs) for molecules known to exist or likely to exist in the nonplanar or *s-cis* conformations. Work initiated on 1,1,3-trichlorobutadiene and analogous compounds will be reported at a later date.

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The Synthesis and Nuclear Magnetic Resonance Spectra of Epimeric 16-Deuterio-17β- and -17α-estradiols[1]

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The synthesis of the 16α- and 16β-deuterio derivatives of 17β- and 17α-estradiol is described. The n.m.r. spectra of the four isomeric structures, with particular reference to the C-17 proton resonance, are discussed. The n.m.r. data permit the drawing of certain conclusions as to the conformation of the steroidal ring D bearing a C-17 hydroxyl substituent.

The synthesis of 17β- and 17α-estradiols stereospecifically labeled at C-16 with deuterium was required in order to study further the conformation of ring D by means of n.m.r. Until now the only n.m.r. data available for a complete series of C-16, C-17 substituted isomers involved carbomethoxy and acetyl substituents.[2] The steric bulk and chemical and electronegative nature of these groups gives rise to interactions which affect the n.m.r. data to such an extent that the values reported can be considered to be specific only for a particular series. The deuterated compounds reported in this paper are particularly suitable for the study of C-17 proton resonance in ring D. The deuterium substitution at C-16 simplifies the ABX pattern of the 17-proton to the AX which permits a more precise analysis of the H-16, H-17 coupling constants. At the same time the size of the isotope does not lead to steric distortion of ring D.[3] Furthermore the chemical and electronegative character of the substituent is essentially indistinguishable from hydrogen so that complications from these factors are avoided. The aromatic ring A is another advantage, since the chemical shift of the 17-proton is now unique in the molecule. The deuterated series could be used as a standard with which n.m.r. studies of otherwise substituted D-ring may be compared. The knowledge obtained may permit the application of n.m.r. to the difficult problem of ring-D conformation.

The synthetic sequences developed with these compounds where the orientation of the isotope can be demonstrated by physical means should then be applicable to reactions in which tritium is the isotope desired. These radioactive compounds would then be available for the study of biochemical pathways of the metabolism of the female sex hormone, with certainty that the isotope was in the correct position in the molecule.

In order to ensure stereospecificity, the synthesis of both the 16α- and 16β-deuterated compounds was achieved by two alternative stereoselective procedures. Introduction of the deuterium in the 16β-position was effected by the following methods. The readily available 16α-hydroxyestrone (Ia)[4] was converted to the ditosylate Ib which was then reduced with $LiAlD_4$. This reduction proceeds with inversion[5] to give the 16β,17α-dideuterio-17β-estradiol (IIa). The latter was converted to the 3-monobenzoate IIc and oxidized with the Jones reagent[6] to give 16β-deuterioestrone benzoate (IIIa) which was reduced with $LiAlH_4$ to give the desired 16β-deuterio-17β-estradiol (IVa). A second sequence was $LiAlD_4$ reduction of the 16α,-17α-epoxide V[7] to give 16β-deuterio-17α-estradiol (VIa). The phenolic group was protected as the benzoate VIc and oxidation of the 17α-hydroxy group with the Jones reagent[5] proceeded without loss of

(1) This work was supported by a grant from the American Cancer Society and a research grant (CA 07304-1) from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service.

(2) A. D. Cross and P. Crabbe, *J. Am. Chem. Soc.*, **86**, 1221 (1964).

(3) See, for instance, A. D. Cross and C. Beard, *ibid.*, **86**, 5317 (1964).

(4) W. R. Biggerstaff and T. F. Gallagher, *J. Org. Chem.*, **22**, 1220 (1957).

(5) G. K. Helmkamp and B. F. Rickborn, *ibid.*, **22**, 479 (1957).

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

(7) V. Prelog, L. Ruzicka, and P. Wieland, *Helv. Chim. Acta*, **28**, 250 (1945).

isotope[8] to give 16β-deuterioestrone benzoate (IIIa), which upon $LiAlH_4$ reduction then gave 16β-deuterio-17β-estradiol (IVa) identical by infrared and n.m.r. with that prepared by the previous route. The coincidence of the two products and the stereospecific nature of the second procedure suggest that the reduction of the 16α-tosylate with $LiAlD_4$ proceeded with inversion of better than 90%. Epimerization of the 17β-hydroxy group of IVa was also accomplished without affecting the deuterium, employing the recent procedure of Henbest.[9] The C-17 tosylate IVb was prepared, treated with tetrabutylammonium acetate, and after hydrolysis gave the epimeric 16β-deuterio-17α-estradiol (VIa), identical with the compound prepared by the alternative way.

The introduction of the 16α-deuterium proved to be somewhat more involved. Reduction of the 16β,-17β-epoxide was not applicable since in this instance hydride attack is exclusively at C-17.[10] The tosylate of 16β-hydroxyestrone could not be prepared because of the great instability of this ketol.[4] However, estra-1,3,5(10)-triene-3,16β,17α-triol 3,17-diacetate (VIIa), obtained by the acetolysis of the 16β,17β-epoxide,[11] gave the desired 16β-tosylate VIIb. Reduction of VIIb with $LiAlD_4$, however, did not proceed with inversion as expected but gave a product identical with 16β-deuterio-17α-estradiol (VIa). Undoubtedly the deuteride attack at C-16 was preceded by the formation of a 16α,17α-cyclic intermediate with double inversion and over-all retention of configuration at C-16. Despite attempts to vary the conditions, at best only mixtures of 16α- and 16β-deuterated compounds were obtained.

The mechanism of $LiAlH_4$ reduction of enol acetates has been studied by Dauben,[12] whose results suggested a *cis* cyclic intermediate complex which is then attacked by the protonating agent. Since $LiAlH_4$ reduction of estrone enol diacetate gave 17β-estradiol almost exclusively and if the mechanism suggested were applicable to ring D, a suitable stereoselective route to the 16α-deuterated compound was available. Estrone enol diacetate (VIII) was treated with $LiAlH_4$ and the complex was destroyed with a dilute solution of deuterioacetic acid in D_2O. A 16α-deuterio-17β-estradiol (IVc) was obtained which proved to be different from the 16β isomer by both infrared and n.m.r. A second successful stereoselective synthesis of the 16α-deuterio compounds was accomplished by catalytic reduction of estrone enol diacetate (VIII) in dimethoxyethane with deuterium which proceeded rapidly to give after hydrolysis the product of *cis* addition, 16α,-17α-dideuterio-17β-estradiol (IIb). This was carefully purified from some accompanying 17α-diol, benzoylated at C-3 (IId), and oxidized with the Jones reagent to the 16α-deuterio-17 ketone IIIb. Reduction of IIIb with $LiAlH_4$ gave 16α-deuterio-17β-estradiol (IVc). The 16α-deuterio-17α-diol VIb was then obtained by epimerization of the tosylate IVd with tetrabutylammonium acetate and subsequent hydrolysis. The same reaction sequence was applied to IVc prepared by hydride reduction of VIII. Both compounds were identical by infrared and n.m.r.

For comparison purposes, it was desirable to have the 16-dideuterated compounds. These were obtained by equilibrating estrone in a solution of NaOD in D_2O, to give 16,16-dideuterioestrone. Reduction of the dideuterated product with $LiAlH_4$ gave the dideuterated 17β-estradiol IVe, which on epimerization of the 17-tosylate led to the dideuterio-17α-diol VId. For n.m.r. study all of the deuterated estradiols were converted to their diacetates.

It is pertinent to note that while there are differences in the positions of the deuterium bands in the infrared for the various compounds, these are so small that they are not suitable for reliable structural assignments.

N.m.r. Studies. The n.m.r. values for the 17-proton which were obtained for the various compounds prepared in this study are listed in Table I. The chemical shift data permit ready distinction between the 17α- and 17β-acetates, with the 17α-proton resonating *ca.* 10 c.p.s. upfield of the 17β-proton. This difference, relatively small compared with the difference in epimers of six carbon rings,[13] may be a consequence of the semiaxial and semiequatorial nature of the bonds at C-17. This separation between the 17α- and 17β-protons is retained unchanged despite the change in chemical shift in the tosylate derivatives. This, plus the constancy of the coupling constants of C-17 proton in the two esters, would indicate that the size of the ester group at C-17 does not effect any major change in the shape of ring D.

Table I. N.m.r. Values for the 17-Proton[a]

D-Ring substituents	Chemical shift, c.p.s.	$J_{H-16-H-17}$, c.p.s.
17β-AcO	277	Triplet
17α-AcO	288	6.0 (d)
17α-TsO	269	5.5 (d)
16β-D, 17β-AcO	277	9.0 (d)
16β-D, 17β-TsO	260	9.0 (d)
16α-D, 17β-AcO	277	6.5[b] (d)
16α-D, 17β-TsO	260	6.5 (d)
16β-D, 17α-AcO	288	(s)
16β-D, 17α-TsO	269	(s)
16α-D, 17α-AcO	288	6.5 (d)
16α-D, 17α-TsO	269	6.0 (d)
16α-, 16β-D, 17β-AcO	277	(s)[b]
16α-, 16β-D, 17α-AcO	288	(s)

[a] The spectra were obtained at 60 Mc.p.s., on a Varian A-60 spectrometer, in carbon tetrachloride containing tetramethylsilane (TMS) as an internal standard. Chemical shifts are quoted as c.p.s. downfield from TMS (0.0 c.p.s.) and are accurate to ±1 c.p.s. Coupling constants *J* also expressed in c.p.s. are accurate to ±0.5 c.p.s. Abbreviations used are AcO = CH_3COO–, TsO = *p*-$CH_3C_6H_4SO_3$–, D = ^2H, d = doublet, s = singlet. [b] These bands were broadened due probably to H–D coupling.

The correlation of dihedral angles with observed coupling constants as defined by the Karplus equation[14] has been widely applied to conformational problems in six-membered rings, including those in steroids. Indiscriminate use of the Karplus equation and its modi-

(8) This point is important since epimerization could occur in the ketonic derivative. When the corresponding tritium-substituted compounds were oxidized under these conditions, no change of specific activity was observed in either the 16β or 16α derivatives.

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

(10) J. Fishman and W. R. Biggerstaff, *J. Org. Chem.*, **23**, 1190 (1958).

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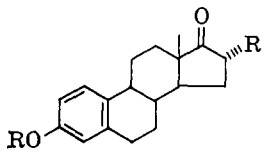
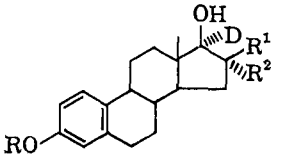
(14) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

fications has resulted in justified criticism,[15] particularly with respect to the determination of accurate dihedral angles from observed coupling constants. At the present state of knowledge, it appears that only the general shape of the curve of the Karplus equation can be used with confidence and that only gross values for dihedral angles can be calculated from coupling constants. Although it had been demonstrated that the Karplus equation retains validity in the five-carbon ring,[16] and indeed has been used in several cases[17] for the solution of structural problems in the pentacyclic ring, its application in these cases should be exercised with at least the same degree of caution as in the six-membered rings. It is only in the light of these comments that the observed coupling constants of the C-17 proton can be applied to the problem of steroid ring-D conformation.

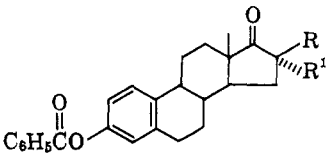
Recently,[2] from Dreiding models, Cross has measured, the H-16, 17-dihedral angles for the three possible conformations of ring D suggested by Brutcher.[18]



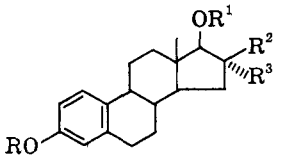
Ia, R = H
b, R = Ts



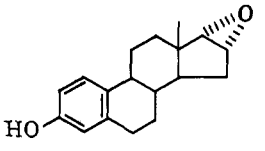
IIa, R = R² = H; R¹ = D
b, R = R¹ = H; R² = D
c, R = C₆H₅CO; R¹ = D; R² = H
d, R = C₆H₅CO; R¹ = H; R² = D



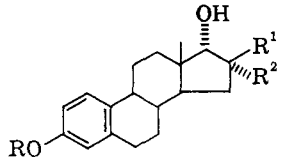
IIIa, R = D; R¹ = 4
b, R = H; R¹ = D



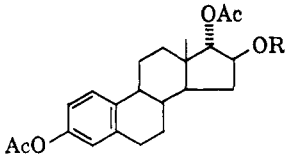
IVa, R = R¹ = R³ = H; R² = D
b, R = C₆H₅CO; R¹ = Ts; R² = D; R³ = H
c, R = R¹ = R² = H; R³ = D
d, R = C₆H₅CO; R¹ = Ts; R² = H; R³ = D
e, R = R¹ = H; R² = R³ = D



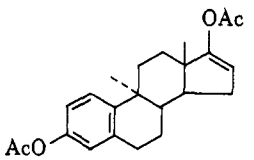
V



VIa, R¹ = D; R = R² = H
b, R² = D; R = R¹ = H
c, R = C₆H₅CO; R¹ = D; R² = H
d, R = H; R¹ = R² = D



VIIa, R = H
b, R = Ts



VIII

From the measured angles the coupling constants were then calculated by the Karplus equation. These calculated values are listed in Table II and are compared with the experimental values obtained in this present study. One anomaly is immediately apparent. It is clear from models that for any possible common ring-D conformation, the dihedral angle between the 16α,-17α-protons should be close to that of the 16β,17β-pair. Since all other variables are constant, it is only reasonable to expect that the coupling constants should be similar, yet this is clearly not the case. The 16α,-17α-coupling is substantially larger than that of the 16β,17β. A recent communication by Williams and Bhacca[19] provides a possible explanation for this discrepancy. These authors have shown that in the cyclohexane ring for the same dihedral angle, the coupling constant of a proton on a carbon bearing an equatorial hydroxyl is 2–3 c.p.s. larger than that of a proton on a carbon bearing an axial hydroxyl. If these findings are extended to the cyclopentane ring and the equatorial and axial character of the 17β- and 17α-bonds is considered the large difference between the 16α,17α- and 16β,17β-coupling constants can be rationalized. It is clear from the data of Williams and Bhacca[19] that insofar as the Karplus equation is concerned, the smaller coupling constant gives a reasonable dihedral angle. By this criterion, the experimental coupling constants observed for the 16α,17α- and 16β,17α-protons should be reduced for comparison with those derived from the Karplus equation. Since the Williams and Bhacca effect[19] is associated with the orientation difference and the character of the bonds at C-17 is only semiaxial and semiequatorial, the 16α,17α- and 16β,17α-coupling constants should be reduced by an indeterminate value up to 2 c.p.s., the lower limit of the effect in the cyclohexane ring.

From the calculated values of Cross[2] in Table II, it is evident that the only significant difference in coupling constants between the three conformations are those for the two *trans*-16β,17α- and -16α,17β-couplings in the envelope conformation C. It is

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(18) F. V. Brutcher and W. Bauer, *J. Am. Chem. Soc.*, **84**, 2236 (1962).
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Table II. Calculated and Observed $J_{H-16-H-17}$[a]

H-16–H-17 configuration	A	B	C	J, found
16β,17α	5.9–7.1	3.7–5.0	0.5–1.4	6.5
16α,17β	0.3–0.0	0.3–0.8	2.4–3.7	0.0
16β,17β	5.7–6.7	7.5–7.9	7.8–8.2	6:5
16α,17α	6.2–6.9	7.8–8.0	7.9–8.1	9:0

[a] All J values are in c.p.s. and are correct to ±0.5 c.p.s.

gratifying that comparison of the calculated with the observed values in Table II, shows that only the two *trans* couplings are different from those calculated for the C conformation. It would appear, then, that this conformation can be eliminated from consideration in the geometry of ring D. This suggestion is further supported by the good agreement of the observed values with those calculated for the other two conformations A and B. Due to the limitation of the Karplus equation, mentioned previously, no definite choice between the two remaining conformations is possible from the available data. Since the divergent constants of the C conformation include ring D with 17α- and 17β-substituents, it does not appear useful to contemplate that in this instance the orientation of the substituent at C-17 caused conformational changes and accounted for the differences.

It must be emphasized that the coupling constants measured apply with certainty only to ring D bearing only a 17-hydroxy group whether free or esterified, a structure which includes the important male and female sex hormones. These values may not apply to ring D with other substituents which may cause ring distortions. It is to be hoped, however, that the present data derived from the simplest substituted ring D, commensurate with n.m.r. analysis can serve as a criterion by which other substituents on the n.m.r. spectra of ring D can be measured and, with increasing knowledge, be correctly interpreted.

Experimental[20]

17-Oxoestra-1,3,5(10)-triene-3,16α-diol Ditosylate (Ib). To a solution of 43 mg. of 16α-hydroxyestrone Ia in 2.5 ml. of pyridine was added 0.3 g. of *p*-toluenesulfonyl chloride. After standing overnight at room temperature the solution was poured into excess ice-cold 5% sulfuric acid solution and extracted well with ether. The ethereal layer was washed with sodium bicarbonate solution, then water, dried, and evaporated. The oily residue was purified by chromatography on acid-washed alumina. Elution with benzene gave an oil which crystallized from petroleum ether (b.p. 30–60°)–acetone to give the product as plates melting at 152–154°.

Anal. Calcd. for $C_{32}H_{34}O_7S_2$: C, 64.9; H, 5.76. Found: C, 65.2; H, 5.48.

Estra-1,3,5(10)-triene-3,16β,17α-triol 16-Tosylate 3,17-Diacetate (VIIb). A solution of 50 mg. of 3,-16β,17α-estriol diacetate VIIa in 5 ml. of pyridine containing 0.4 g. of *p*-toluenesulfonyl chloride was allowed to stand for 2 hr. at room temperature. After working up the reaction as above, the semicrystalline residue was purified by chromatography on acid-washed alumina. Elution with benzene gave 42 mg. of the product which crystallized from petroleum ether. The analytical sample melted at 135–138°.

Anal. Calcd. for $C_{29}H_{34}O_7S$: C, 66.14; H, 6.51. Found: C, 66.40; H, 6.29.

16β-Deuterioestra-1,3,5(10)-triene-3,17β-diol (IVa).

A. By $LiAlD_4$ Reduction of Tosylate Ib. To a solution of 100 mg. of 16α-hydroxyestrone ditosylate Ib in 25 ml. of tetrahydrofuran was added a suspension of 75 mg. of lithium aluminum deuteride in 5 ml. of tetrahydrofuran. The mixture was refluxed for 4 hr., and the excess reagent was decomposed by the addition of water. Dilute sulfuric acid was then added until the pH reached 2 and the suspension was well extracted with ether, which was washed with sodium bicarbonate solution and water. After drying and evaporating the solvent, the residue was purified by quantitative, thin layer chromatography on silica in the system 75% ethyl acetate–25% cyclohexane, to give 38 mg. of *16β,17α-dideuterio-17β-estradiol* (IIa) which showed no H-17 absorption in the n.m.r. spectrum. The dideuterio derivative IIa was now dissolved in 15 ml. of 5% sodium hydroxide solution and 0.2 ml. of benzoyl chloride was added. After 5 min. of vigorous shaking, the flocculent precipitate of 16β,17α-dideuterioestra-1,3,5(10)-triene-3,17β-diol 3-benzoate (IIc) was filtered off. Without further purification the dried benzoate (IIc) was dissolved in 5 ml. of acetone and cooled to 0° in ice bath. Jones reagent (2 drops) was then added with stirring, and the reaction mixture was allowed to stand at 0° for 8 min. Water then was added and the aqueous suspension was extracted with ether, which in turn was washed with cold sodium bicarbonate solution and water, dried, and evaporated. The residue was crystallized from petroleum ether–acetone to give 30 mg. of *16β-deuterioestrone benzoate* (IIIa), m.p. 221–224°. A 25-mg. sample of the benzoate IIIa was dissolved in 20 ml. of ether. The solution was cooled to 0° in an ice bath, and an ethereal solution of 15 mg. of lithium aluminum hydride was added dropwise with stirring. After stirring at 0° for 30 min., the reaction was worked up in the usual manner to give 18 mg. of *16β-deuterio-17β-estradiol* (IVa) recrystallized from benzene containing a trace of ethanol. The infrared spectrum of IVa showed a strong deuterium band at 2178 cm.$^{-1}$. The diacetate derivative was prepared in the usual manner and also exhibited the deuterium band at 2176 cm.$^{-1}$ in the infrared. The n.m.r. spectrum of the diacetate showed three 3-proton singlets at 47 (18-CH_3), 117 (17-acetate), and at 131 c.p.s. (3-acetate). The 17α-proton appeared as a doublet J = 9 c.p.s. centered at 277 c.p.s.

B. By $LiAlD_4$ Reduction of the Tosylate VIIb. A 150-mg. sample of the 16β-tosylate VIIb was reduced as above with $LiAlD_4$. The product weighing 68 mg. was the 16β-deuterio-17α-estradiol (VIa), which was converted to the benzoate VIc and oxidized with the Jones reagent to 16β-deuterioestrone benzoate (IIIa) by procedures detailed above. Reduction of IIIa with $LiAlH_4$ gave 16β-deuterio-17β-estradiol (IVa) identical by infrared and n.m.r. with that prepared by route A.

(20) The melting points were obtained on a Kofler stage and are corrected. The infrared spectra were obtained in potassium bromide. The analyses are by Spang Microanalytical Laboratory, Ann Arbor, Mich.

C. By $LiAlD_4$ Reduction of the 16α,17α-Epoxide V. A 100-mg. sample of 16α,17α-epoxyestra-1,3,5(10)-triene-3-ol (V) in 25 ml. of tetrahydrofuran was refluxed for 4 hr. with 50 mg. of $LiAlD_4$. The usual work-up gave 78 mg. of 16β-deuterio-17α-estradiol (VIa), which again was converted to the benzoate VIc, oxidized to IIIa, and reduced with $LiAlH_4$ to give 16β-deuterio-17β-estradiol (IVa), identical with that prepared by routes A and B.

16β-Deuterioestra-1,3,5(10)-triene-17α-ol. A. By the $LiAlD_4$ Reduction of 16α,17α-Epoxide V. The reduction described above (C) was repeated and 16β-deuterio-17α-estradiol (VIa) was recrystallized from benzene. The compound showed a deuterium band in the infrared at 2182 $cm.^{-1}$. The diacetate obtained in the usual manner also exhibited the deuterium band at the same position. The n.m.r. spectrum of the diacetate showed three 3-proton singlets at 47 (18-CH_3), 117 (17-acetate), and 131 c.p.s. (3-acetate). The 17β-proton appeared as a singlet at 288 c.p.s. The width at half-height was 1.5 c.p.s.

B. By the $LiAlD_4$ Reduction of the Tosylate VIIb. The product of this reaction as described above (B) and its diacetate derivative were identical both by infrared and n.m.r. with 16β-deuterio-17α-estradiol obtained by route A.

C. By Epimerization of 16β-Deuterioestradiol 3-Benzoate 17β-Tosylate (IVb). A 150-mg. sample of 16β-deuterio-17β-estradiol (IVa) was converted to the 3-benzoate which was then dissolved in 5 ml. of pyridine and treated with 600 mg. of *p*-toluenesulfonyl chloride. After standing overnight at room temperature, the reaction was worked up in the usual manner to give the 182 mg. of the 17-tosylate derivative IVb which crystallized from petroleum ether–acetone as needles, m.p. 185–188°.

Anal. Calcd. for $C_{32}H_{35}O_5S$: C, 72.40; H, 6.58. Found: C, 72.18; H, 6.34.

The n.m.r. spectrum showed two 3-proton singlets at 50 (18-CH_3) and 147 c.p.s. (aromatic CH_3). The 17α-proton appeared as a doublet centered at 260 c.p.s., J = 9 c.p.s.

A 170-mg. sample of the tosylate IVb was dissolved in 10 ml. of N-methylpyrrolidone and 1.0 g. of tetrabutylammonium acetate was added. After heating at 160° for 3 hr., the dark solution was poured into cold sodium chloride solution and the mixture was extracted with ether, which was washed with sodium bicarbonate solution and water, dried, and evaporated. The oily residue was then hydrolyzed by refluxing for 2 hr. in 5% ethanolic KOH. The product of the hydrolysis was purified by quantitative, thin layer chromatography on silica in 1:1 ethyl acetate–cyclohexane. Elution of the 17α-estradiol zone gave 28 mg. of 16β-deuterio-17α-estradiol (VIa) which was converted to the diacetate. Both VIa and its deriyative were identical with those obtained by routes A and B.

16α-Deuterioestra-1,3,5(10)-triene-17β-ol (IVc). A. By $LiAlH_4$ Reduction of Estrone Enol Diacetate (VIII). A solution of 100 mg. of enol diacetate VIII in 10 ml. of tetrahydrofuran was added slowly to a stirred, ice-cold suspension of 40 mg. of $LiAlH_4$ in 5 ml. of tetrahydrofuran. After stirring at 0° for 1 hr., the suspension was added slowly with cooling to a solution of deuterioacetic acid in deuterium oxide (prepared by reaction 5 ml. of acetic anhydride with 2 ml. of deuterium oxide). After the usual work-up the residue was purified by quantitative, thin layer chromatography on silica in 1:1 ethyl acetate–cyclohexane. The 17β-estradiol zone was carefully isolated and eluted to give 16α-deuterio-17β-estradiol (IVc). The infrared spectrum showed a deuterium absorption at 2185 $cm.^{-1}$ and was different in the fingerprint region from the 16β-deuterio epimer IVa.

The diacetate of IVc was prepared in the usual manner; the infrared deuterium band was at 2190 $cm.^{-1}$, and its n.m.r. spectrum showed three 3-proton singlets at 47, 117, and 131 c.p.s., with the same assignments as before. The 17α-proton appeared as a doublet at 277 c.p.s., J = 6.5 c.p.s.

B. By D_2 Reduction of Estrone Enol Diacetate VIII. A 200-mg. sample of enol diacetate VIII dissolved in 20 ml. of dimethoxyethane was reduced with deuterium over 50 mg. of 10% palladium on charcoal. Deuterium uptake ceased after 10 min. and 16α,17α-dideuterioestradiol diacetate, which was isolated in quantitative yield, showed no 17-proton absorption in the n.m.r. The 16α,17α-dideuterio-1,3,5(10)-estratriene-3,17β-diol diacetate was hydrolyzed by standing overnight in 25 ml. of 5% ethanolic potassium hydroxide. The isolated 16α,17α-dideuterio-17β-estradiol (IIb) was converted to the 3-benzoate (IId) and oxidized to the estrone derivative IIIb by procedures described previously. Reduction with $LiAlH_4$ of IIIb gave 16α-deuterio-17β-estradiol (IVc) which was identical with that obtained by route A.

16α-Deuterioestra-1,3,5(10)-triene-17α-ol (VIb). A 150-mg. sample of the 16α-deuterioestradiol IVc was converted in turn to the 3-benzoate and then to the 17-tosylate IVd by the usual procedures described above. Epimerization of tosylate IVd with tetrabutylammonium acetate gave, after hydrolysis, 34 mg. of 16α-deuterio-17α-estradiol (VIb), the infrared spectrum of which showed deuterium absorption at 2190 $cm.^{-1}$. The diacetate prepared in the usual manner gave an n.m.r. spectrum in which the usual three 3-proton singlets at 47, 117, and 131 c.p.s. were present. The 17β-proton now appeared as a doublet at 288 c.p.s., J = 6.5 c.p.s. The ditosylate was also prepared the n.m.r. spectrum of which showed the 17-proton doublet at 269 c.p.s., J = 6 c.p.s.

16α,16β-Dideuterioestra-1,3,5(10)-triene-17β-ol (IVe). A 300-mg. sample of estrone was added to a solution prepared from 0.2 g. of sodium and 15 ml. of D_2O. The mixture was stirred and heated on a steam bath for 3 hr. The cooled reaction mixture was filtered and the filtrate was acidified with deuterioacetic acid. The precipitated dideuterioestrone was filtered, dried, and reduced with $LiAlH_4$ in tetrahydrofuran. The isolated 16-deuterated 17β-estradiol IVe showed deuterium bands at 2218, 2120, and 2185 $cm.^{-1}$ in the infrared. The n.m.r. spectrum of the diacetate showed the 17β-proton as a singlet at 277 with a half-height width of 2.3 c.p.s.

16α,16β-Dideuterioestra-1,3,5(10)-triene-17α-ol (VId). The 16,16-dideuterio-17β-estradiol IVe was epimerized to the 17α-ol VId *via* the 3-benzoyl-17-tosyl derivative as described for the other cases. The infrared spectrum of VId showed deuterium bands at 2120, 2170, and 2270 $cm.^{-1}$, and the n.m.r. spectrum of the

diacetate showed 17β-proton absorption as a singlet at 288 c.p.s. with a half-height width of 1.5 c.p.s.

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Carbonyl-Stabilized Sulfonium Ylids. Reaction with Schiff Bases

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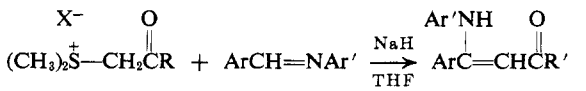
Carbonyl-stabilized sulfur ylids have been prepared via treatment of the corresponding sulfonium salts with sodium hydride. These ylids react with Schiff bases to produce 3-arylaminocinnamate derivatives demonstrating the synthetic potential of this ylid series.

Discussion

The stabilization of carbanions by the inductive and p–d overlap effects of an adjacent phosphorus atom has provided a class of P-ylids which have been shown to provide one of the most useful carbon–carbon bond forming reactions.[1] In the same manner as phosphorus, sulfur may also expand its valence shell utilizing 3d orbitals to stabilize an adjacent carbanion.[2] The synthetic utility of S-ylids has not been as fully explored as the P-ylids. S-Ylids, however, appear to react with carbonyl compounds by initial nucleophilic attack with the elimination of a sulfide whereas the P-ylids eliminate phosphine oxides.[3]

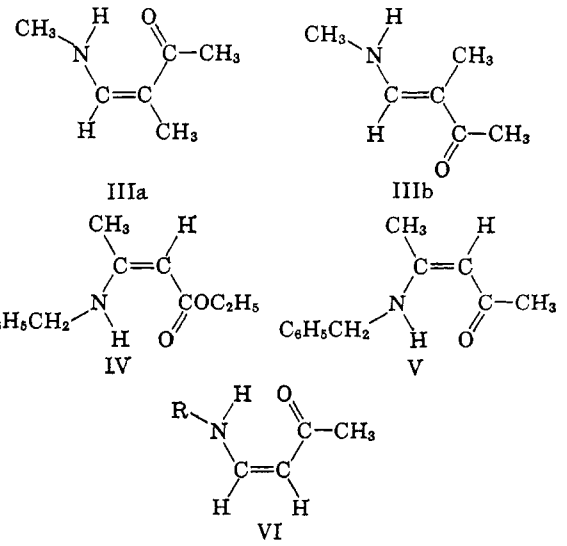
S-Ylids were known as early as 1930,[4] although their reactivity has been studied only recently.[3] Corey[5] has demonstrated that dimethyl sulfonium methylide generated *in situ* provides a valuable synthesis of epoxides *via* reaction with aldehydes and ketones. S-Ylids which are resonance stabilized are known in only one reported instance.[3] Dimethyl sulfonium fluorenylides, generated by the action of base on the corresponding sulfonium salt, are stable, isolable, and undergo reaction with carbonyl compounds. In our continuing study of ylid chemistry[6] we have prepared some sulfonium methylides wherein the carbanion is stabilized by a carbonyl group, a type of ylid which in the phosphorus series is isolable yet reacts with electrophiles.

Treatment of sulfonium salts (I) with sodium hydride in tetrahydrofuran resulted in the evolution of 1 equiv. of hydrogen. Addition of Schiff bases to the ylid *in situ*, followed by a short reflux period, gave 3-arylaminocinnamates and -cinnamamides II in generally good yields. (See Table I.)



I II

The assignment of structure II is made on the basis of elemental and spectral analysis and upon hydrolysis experiments. The n.m.r. values are given in Table II. The presence of a singlet (area = 1) at low field suggests an N–H intramolecularly chelated with a carbonyl oxygen.[7] This is inferred from the large paramagnetic shift of the N–H proton observed in similar β-amino unsaturated carbonyl compounds in comparison to dimedone Schiff bases in which such hydrogen bonding is precluded. The *cis* isomer (IIIa) of 3-methyl-4-methylamino-3-buten-2-one exhibits an N–H singlet at τ 0.5 whereas the *trans* isomer (IIIb) (incapable of N–H hydrogen bonding) shows this proton at 5.0.[8] Consequently, II possesses an N–H proton chelated to



IIIa IIIb

IV V

VI

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