g/l. at pH 6.[9] Thus, this metabolite of tolbutamide, as well as the carboxy metabolite, is very soluble at normal urinary pH values. Both II[11] and III[13] have been reported to have no hypoglycemic activity.

Acknowledgments.—The authors acknowledge the valuable technical assistance of Mr. R. W. Judy and Mr. H. Harpootlian. We are also indebted to members of the Physical and Analytical Chemistry Department for elemental and spectral determinations and to Dr. H. L. Oster for the clinical aspects of this study. Thanks are also due to Dr. A. A. Forist for use of his data on the solubility of 1-butyl-3-*p*-hydroxymethylphenylsulfonylurea and for helpful discussions during the course of this work.

(13) H. Ruschig, G. Korger, W. Aumüller, H. Wagner, R. Weyer, A. Bänler, and J. Scholz, *Arzneimittel-Forsch.*, **8**, 448 (1958).

The Preparation and Chemistry of 9α,10α-Oxidoestra-4-en-3-ones

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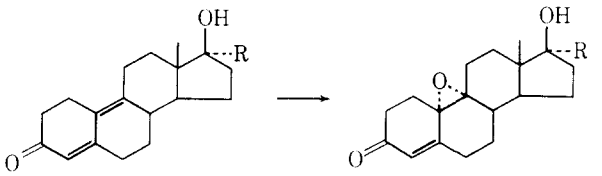
The reaction of estra-4,9(10)-dien-3-ones with peracid affords 9α,10α-oxido compounds in high yield. Upon treatment of the oxides with base or acid, $\Delta^{9(11)}$-estradiols or ethers of these diols, respectively, are obtained. With pyrrolidine the oxides rearranged to yield 3-pyrrolidinoestra-1,3,5(10)-trien-9α-ols and 3-pyrrolidinoestra-1,3,5(10),9(11)-tetraenes. The pharmacology of these compounds is summarized.

The reaction of various estra-4,9(10)-dien-3-ones[1] with peracids results in the preparation of monoepoxides in high yield. Because of the importance of several estrenes or 19-nor steroids in various biological areas, including anabolic[2] and ovulation inhibition,[3] an investigation of the structure, the chemistry, and the pharmacology of these epoxides was undertaken.

The epoxidation of double bonds in a variety of different positions in the steroid nucleus gives oxides whose resultant stereochemistry is frequently attributed to steric factors alone. The epoxidation of the 5(10) double bond of estrenes results in almost exclusive formation of 5β,10β-epoxides.[4] On the other hand, the 9(11) double bond of a number of steroids on epoxidation affords 9α,11α-oxides. A recent example of epoxidation of a possible incipient 9(10) double bond of an estrene was found to yield a 9β,10β-epoxide.[5] This case, however, was not clearly an epoxidation of a 9(10) double bond and could also be the result of β-face attack of peracid at C-10. The reaction of a 9(10) double bond with peracid could then be an indication of the steric factors operating in this system.



Ia, R = H
b, R = CH_3
c, R = C≡CH

IIa, R = H
b, R = CH_3
c, R = C≡CH

The epoxides in this report, which were obtained by reaction of the estra-4,9(10)-dien-3-ones and *m*-chloroperbenzoic acid in about 80% yield, were found to possess 9α,10α stereochemistry indicating α-face attack by the peracid.[6] This epoxidation was carried out with the compounds indicated.

The stereochemistry of the epoxides was not readily apparent using the available physicochemical methods. While the compounds II gave ORD curves similar to that of 10α-testosterone,[7] the effect of oxides at this position in relation to the absorbing chromophore was not known. Further, the conformational mobility of the A ring could also interfere with interpretations of these spectra. The nmr spectra were similarly equivocal showing a broadened 4-vinyl proton[8] with no pronounced shifts of the positions of the 18-methyl protons when compared to the spectrum of the appropriate 19-nortestosterone. Thus, chemical transformations were necessary in order to complete the stereochemical assignment.

Compound IIa was treated with excess lithium aluminum hydride, and the resultant product in turn was treated with manganese dioxide to reoxidize the allylic hydroxyl grouping. The substituted 19-nortestosterone compound obtained was an α,β-unsaturated ketone as evidenced by its ultraviolet spectrum. Examination of its ORD spectrum indicated stereochemistry identical with that of 19-nortestosterone, namely 9α,10β. It has been demonstrated that the 10β-hydroxy grouping does not alter the shape and direction of the ORD curve[4] and similar behavior would be expected for the C-9 hydroxyl substitution.

The known estra-4-ene-10β,17β-diol-3-one[4] was prepared. Although this gave a similar ORD curve, its physical constants differed considerably. Thus IIIa must have the alternate estra-4-ene-9α,17β-diol-3-

(1) M. Perelman, E. Farkas, E. J. Fornefeld, R. J. Kraay, and R. T. Rapala, *J. Am. Chem. Soc.*, **82**, 2402 (1960).

(2) A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953).

(3) O. V. St. Whitelock, *Ann. N. Y. Acad. Sci.*, **71**, 479 (1958).

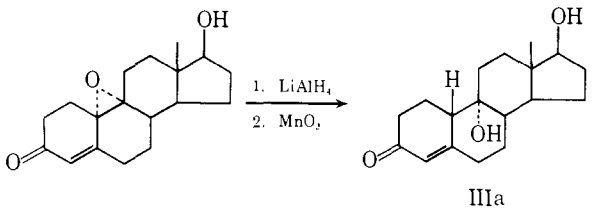
(4) J. P. Ruelas, J. Iriarte, F. A. Kincl, and C. Djerassi, *J. Org. Chem.*, **23**, 1744 (1958).

(5) H. Hasegawa and K. Tsuda, *Chem. Pharm. Bull.* (Tokyo), **12**, 473 (1964).

(6) After our work was completed some related studies were reported by D. Hartley and H. Smith, *J. Chem. Soc.*, 4492 (1964). Only a few portions of the two studies overlap.

(7) (a) R. Wenger, H. Dutler, H. Wehrli, K. Schaffner, and O. Jeger, *Helv. Chim. Acta*, **46**, 1096 (1963). (b) E. Farkas, unpublished results. A similar spectrum was obtained for 10α-19-nortestosterone.

(8) T. A. Wittstruck, S. K. Malhotra, and H. J. Ringold, *J. Am. Chem. Soc.*, **85**, 1699 (1963).



IIIa

one structure, and the oxide, in turn, must have the 9α,10α stereochemistry.

The other epoxides IIb and IIc showed no significant differences in their nmr spectra, except for the added methyl and ethynyl proton peaks, and ORD spectra with those of IIa; thus by analogy to IIa these epoxides also possess the 9α,10α stereochemistry. It is interesting to note that although α,β-oxido ketones led to an inversion of signs in applying Octant rule principles,[9] the present oxides do not appreciably modify the ORD curves of the stereochemically related α,β-unsaturated ketones.

The 9α,10α-epoxides were found to be relatively readily available intermediates for a variety of interesting transformations. The epoxides react rapidly under both acidic and basic conditions. This reactivity can be demonstrated by adding a few drops of dilute potassium hydroxide solution to an ethanolic solution of IIa. Determination of the ultraviolet spectrum of an aliquot sample shows the presence of a typical A-ring phenoxide species. Addition of dilute mineral acid at this point with subsequent ultraviolet determination revealed the presence of still another chromophore, the $\Delta^{9(11)}$-estratrien-3-ol chromophore. Addition of acid alone to the original sample did not result in any reaction under these mild conditions. Attempts to isolate the intermediates to the $\Delta^{9(11)}$-estradiols, presumably the 9α-hydroestradiols, were not successful.

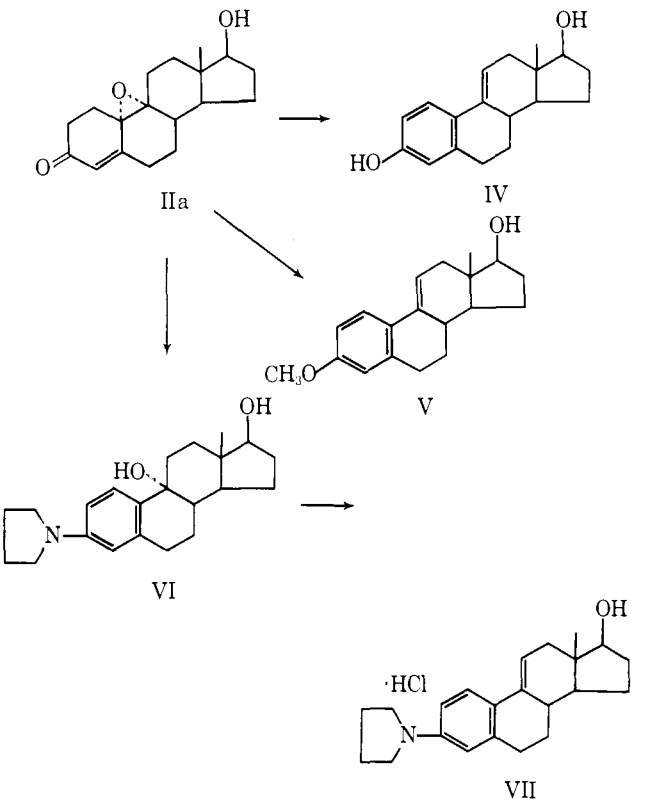
These pilot studies of chemical changes as evidenced by the ultraviolet spectra can be readily transformed to preparative-scale syntheses. Treatment of the epoxide IIa with potassium hydroxide in methanol and subsequent isolation of the product results in a good yield of the $\Delta^{9(11)}$-estradiol (IV) (see Scheme I). Treatment of IIa with acid in methanolic perchloric acid, on the other hand, yields the $\Delta^{9(11)}$-estradiol 3-methyl ether (V). Other ethers can be obtained by using different alcohols as solvent.

The 9α,10α-epoxides can be further treated with various organic amines, particularly with pyrrolidine, in order to obtain 3-amino-substituted aromatic A-ring steroids.[10] Reaction under mild conditions leads to the 9α-hydroxyamines VI, while more vigorous treatment such as a longer reaction time results in formation of the corresponding 9(11)-unsaturated compounds (VII). The 9α-hydroxy compounds can also be dehydrated under mild acid treatment. This dehydration can be readily followed by changes in the ultraviolet spectrum with the prominent maximum shifting from about 259 to about 294 mμ. Because of apparent air oxidation, these latter compounds are most conveniently handled as their acid salts.

(9) C. Djerassi, W. Klyne, T. Norin, G. Ohloff, and E. Klein, *Tetrahedron*, **21**, 163 (1965).

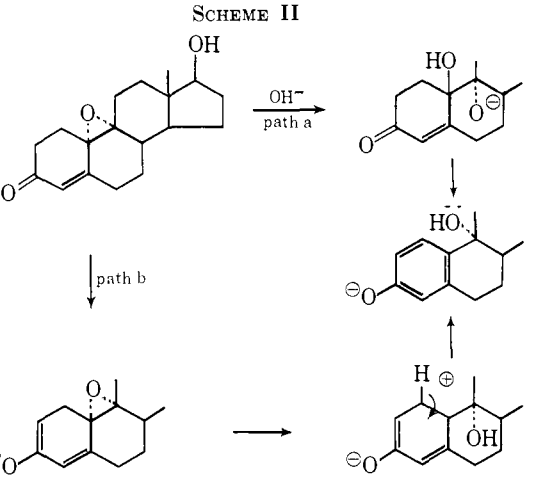
(10) Using somewhat different conditions, a similar compound was reported as the 17-ester by G. Nomine, D. Bertin, R. Bucourt, and A. Pierdet (Roussel-Uclaf), U. S. Patent 3,055,885 (1962).

Scheme I



The facile base-catalyzed reaction can be explained by epoxide opening with hydroxide ion and subsequent aromatization. A more likely mechanism involves enolate formation, opening of the epoxide to form a stabilized carbonium ion at C-10, and finally proton loss resulting in the phenolate species. These changes can occur as stepwise or concerted processes (Scheme II).

Scheme II



The 9α-hydroxy phenoxide anion has been observed in the ultraviolet studies, but the phenol eluded isolation under a variety of different conditions. Under neutral conditions the phenol has been prepared.[11] Reaction under acid conditions can be explained in a similar sequence of reactions.[12]

(11) K. Tsuda, S. Nozoe, and Y. Okada, *Chem. Pharm. Bull.* (Tokyo), **11** 1022 (1963).

(12) F. S. Alvarez and A. B. Rutz, *J. Org. Chem.*, **30**, 2047 (1965).

The pharmacology of these compounds was of some interest. Compound IIa had anabolic activity approximately equal to that of testosterone with diminished androgenicity when studied by subcutaneous administration in the levator ani assay.[13] Surprisingly, the 17α-methyl derivative, IIb, showed no oral anabolic activity at up to 3-mg total dose. The 17α-ethynylestrene IIc was found to have weak progestational activity with a relative potency of one-tenth of 17α-ethynyl-19-nortestosterone.[3] The pyrrolidinoestra-1,3,5(10)-triene-9α,17β-diol VI showed weak uterotrophic activity (<0.001% of estradiol) by subcutaneous administration in the 3-day mouse assay.[14] The dehydrated VII was devoid of estrogenic activity at the doses studied, up to 200-mg total dose. Additional biological studies are currently under way.

Experimental Section[15]

9α,10α-Oxidoestra-4-en-17β-ol-3-one (IIa).—To a solution of 1.0 g of estra-4,9(10)-dien-17β-ol-3-one in chloroform was added 0.86 g of *m*-chloroperbenzoic acid. After standing at room temperature for 2 hr, the solution was poured into slightly acidic NaI solution. A slight excess of solid sodium thiosulfate was added to destroy the iodine color and the mixture was extracted thoroughly with CH_2Cl_2. The combined nonaqueous solution was washed successively with Na_2CO_3 and NaCl solutions. After drying (Na_2SO_4), the solvent was evaporated under reduced pressure and the residue was recrystallized from ethyl ether–petroleum ether to give 0.77 g (74% yield) of oxide:[6] mp 148–149°; λ_{max}^{EtOH} 243 mμ (ε 13,450); ORD (*c* 0.44, dioxane), $[\phi]_{389}$ −1030° (T), $[\phi]_{362}$ −597° (T), $[\phi]_{351}$ +1230° (P), $[\phi]_{338}$ +2180° (P), $[\phi]_{326}$ +2110° (P), $[\phi]_{280}$ +400°.

17α-Methyl-9α,10α-oxidoestra-4-en-17β-ol-3-one (IIb) was prepared in a similar fashion in 77% yield, mp 196–198°, λ_{max}^{EtOH} 244 mμ (ε 13,250).

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.51; H, 8.46.

17α-Ethynyl-9α,10α-oxidoestra-4-en-17β-ol-3-one (IIc) was prepared as above in 77% yield and had mp 230–233°, λ_{max}^{EtOH} 243 mμ (ε 13,100).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.89; H, 7.74. Found: C, 76.68; H, 7.68.

Estra-4-ene-9α,17β-diol-3-one (IIIa).—9α,10α-Oxidoestra-4-en-17β-ol-3-one (0.2 g) in dry tetrahydrofuran (THF) was stirred at reflux with 0.18 g of $LiAlH_4$. After the usual work-up the products were extracted into chloroform–THF. The combined solution was washed with NaCl solution and dried (Na_2SO_4), and the solvent was evaporated under vacuum. The crude residue was dissolved in chloroform and treated at reflux with stirring with 2.0 g of MnO_2 overnight. The solids were filtered off and the solvent was evaporated under reduced pressure. The crude residue was dissolved in 10% $CHCl_3$–ethyl ether and chromatographed on 30 g of neutral Grade I alumina. Crystalline material was obtained with $CHCl_3$ as eluent in fractions 31–36. After the fractions were combined, the material was recrystallized from ethyl ether, mp 191–193°, λ_{max}^{EtOH} 242 mμ (ε 13,800).

Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.44; H, 9.03. Found: C, 74.42; H, 9.07.

Estra-4-ene-10β,17β-diol-3-one.—Following essentially the published procedure,[4] the 10β-hydroxy compound was prepared by epoxidation of 0.4 g of estra-5(10)-en-17β-ol-3-one with *m*-chloroperbenzoic acid. The 5β,10β-epoxide (0.1 g, mp 201–204°) was hydrolyzed in 15 ml of 5% KOH in methanol, yielding after appropriate work-up a product with mp 209–212°, λ_{max}^{EtOH} 235 mμ (ε 13,190).

Estra-1,3,5(10),9(11)-tetraene-3,17β-diol (IV).—The 9α,10α-oxido compound IIa (0.1 g) was dissolved in 20 ml of 5% KOH in methanol and the solution was maintained at reflux for 1 hr. It was then poured into 120 ml of 5% HCl, and the mixture was extracted thoroughly with several portions of CH_2Cl_2. The combined nonaqueous solution was washed with saturated NaCl solution and dried (Na_2SO_4), and the solvent was evaporated under reduced pressure. The residue was recrystallized from methanol–water yielding 0.07 g (74% yield) of material, mp 188–189°,[11] λ_{max}^{EtOH} 263 mμ (ε 16,700).

Estra-1,3,5(10),9(11)-tetraene-3,17β-diol 3-Methyl Ether (V).—In a small flask was placed 0.1 g of IIa in 2 ml of reagent methanol and 1 drop of 70% $HClO_4$ was added. After standing at room temperature for 24 hr, the solution was poured into excess cold water and extracted thoroughly with ethyl ether. The combined ethereal solution was washed successively with $NaHCO_3$ and NaCl solutions. After drying, the solvent was evaporated under reduced pressure and the residue was recrystallized from methanol to give crystalline rods, mp 71–73°, λ_{max}^{EtOH} 263 mμ (ε 17,700).

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.50. Found: C, 80.07; H, 8.58 (after drying).

3-(1-Pyrrolidino)estra-1,3,5(10)-triene-9α,17β-diol (VI).—Using a Dean–Stark trap, 0.1 g of IIa in 30 ml of dry benzene, 5 ml of pyrrolidine, and 10 mg of *p*-toluenesulfonic acid was heated at reflux overnight. The solvent was evaporated under vacuum and the residue was taken up in ether. After washing the latter solution successively with $NaHCO_3$ and NaCl solutions, it was dried (Na_2SO_4). The solution was then filtered and concentrated to yield 0.071 g (60%) of material, mp 158–160°, λ_{max}^{EtOH} 259 mμ (ε 22,950). The nmr spectrum contained no vinyl protons.

Anal. Calcd for $C_{22}H_{31}NO_2$: C, 77.37; H, 9.15; N, 4.10. Found: C, 77.48; H, 9.03; N, 4.38.

3-(1-Pyrrolidino)estra-1,3,5(10),9(11)-tetraen-17β-ol Hydrochloride (VII).—The 9α-hydroxy compound VI (0.3 g) was dissolved in 20 ml of reagent methanol, and then 6 drops of concentrated HCl was added. After standing at room temperature overnight, ether was added while cooling in an ice bath to give 0.19 g (60% yield) of product, mp 185–190° dec, λ_{max}^{EtOH} 295 mμ (ε 26,800). Apparently, because of the weakly basic nature of this compound, the hydrochloride must dissociate in ethanol solution since the ultraviolet spectrum of the free base was obtained.

Anal. Calcd for $C_{22}H_{29}NO \cdot HCl$: C, 73.40; H, 8.40; N, 3.89. Found: C, 73.40; H, 8.55; N, 3.59.

Acknowledgment.—We wish to express our thanks to our colleagues in microanalysis, physical chemistry, and pharmacology, who obtained the data referred to in this paper. We particularly acknowledge Mr. L. G. Howard, who helped in the ultraviolet spectroscopy studies.

(13) L. Hershberger, E. Shipley, and R. Meyer, *Proc. Soc. Exptl. Biol. Med.*, **83**, 175 (1953).

(14) B. L. Rubin, A. S. Dorfman, L. Black, and R. I. Dorfman, *Endocrinology*, **49**, 429 (1951).

(15) Melting points were obtained on a Fisher-Johns block and are corrected. The nmr spectra were obtained using an HR60 Varian instrument with $CDCl_3$ as solvent and TMS as an internal standard. The ORD spectra were obtained with a Rudolph 260 instrument.