

calves. Similarly, the expression of IF induction and antiviral activity with other analogues, such as substituted 6-aryl and 6-heterocyclic derivatives, has established a diverse structure-activity relationship. Efforts in both of these areas of interest are in progress and will be reported in due course.

Acknowledgment. We thank B. D. Tiffany and R. L. Johnson for scale-up preparations of several of the pyrimidinones.

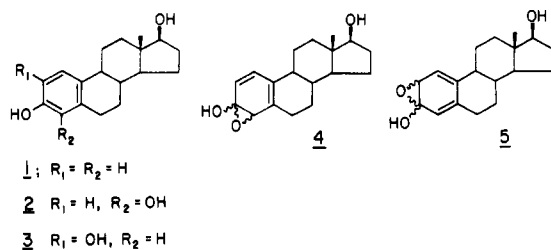
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Biomimetic Synthesis of Catechol Estrogens: Potentially Mutagenic Arene Oxide Intermediates in Estrogen Metabolism¹

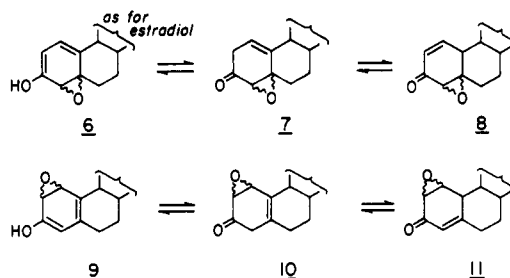
Sir:

Exogenous estrogens have the clear potential to be a causal factor in the development of neoplasms at certain organ sites where such hormones are metabolized.² Though the mechanism for such an initiation remains obscure, it is possible that the pathways in estrogen metabolism generate reactive intermediates capable of binding to the observed cytoplasmic and nuclear receptors.³ Metabolism of estradiol (1), for example, leads to the

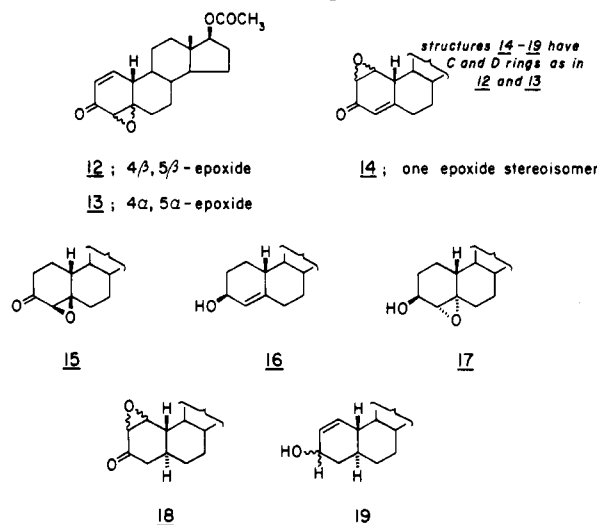


catechols 2 and 3. Arene oxide derivatives of 1 may be intermediates in this metabolism, in analogy to the arene oxides of polycyclic aromatic hydrocarbons, which have been implicated in the carcinogenic effects of these compounds.^{4,5}

Catechol formation through phenolic arene oxides might, a priori, proceed either via oxirane hemiacetals, such as 4 and 5, or via dienol epoxides and their keto tautomers, e.g., 6-8 and 9-11. The oxirane hemiacetals 4 and 5 are intrinsically interesting but have no known simpler counterparts and, if formed, would be expected to be of such



a highly reactive and transient nature that proof of their existence may be difficult and equivocal. Intermediates 6 and 9, however, are capable of stabilization as the keto tautomers 7, 8, 10, and 11. Several workers⁶ have suggested the involvement of dienol epoxides in the formation of catechols from estrone and have demonstrated covalent binding of such estrogens to nucleic acids in the presence of cytochrome P-448 monooxygenase. As an initial investigation of the intermediates in catechol estrogen formation, we have focused on compounds of the conjugated enone series (8 and 11). We now report the synthesis and aromatization of the enone epoxides 12-14.⁷



Compound 12 was synthesized from 19-nortestosterone essentially according to a procedure developed by Mihailovic and his co-workers.⁸ Treatment of 19-nortestosterone with alkaline hydrogen peroxide, followed by acetylation, gave the epoxide 15. The β -epoxide stereochemistry is in accord with expectations based upon work by Burgess⁹ and by Jeger and his co-workers.¹⁰ Dehy-

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- (10) Compounds 12 had mp 114-115 °C; $[\alpha]_D^{25}$ (EtOH) +261.3°; IR (film) ν_{max} 3050, 2950, 1730, 1680, 1620, 1250, 1050, 1030 cm^{-1} ; 1H NMR ($CDCl_3$) δ 0.87 (3 H, s, C-18 Me), 2.03 (acetoxy Me), 3.23 (1 H, m, 4-H), 4.6 (1 H, br t, 17-H), 5.93 (1 H, br d, 2-H), 6.76 (1 H, dd, $J = 10$ and 6 Hz, 1-H). Structure 12 was assigned earlier (ref 9) to a compound reported as an oil. This compound and all other new compounds gave satisfactory elemental and spectroscopic analyses.

drogenation of 15 proceeded cleanly only with selenium dioxide in neutral, strictly anhydrous *tert*-butyl alcohol to give 12.¹⁰ Compound 13 was prepared by reaction of 17-acetyl-19-nortestosterone with iodine-potassium iodate,¹¹ followed by selenium dioxide dehydrogenation as above. Alternatively, epoxidation of the known alcohol 16 with *m*-chloroperbenzoic acid gave 17, although in minor amount compared to the isomeric β -epoxides.¹² Chromium trioxide-pyridine oxidation of 17, followed by selenium dioxide dehydrogenation, gave 13.¹³

Dehydrogenation of 17 β -hydroxy-19-nor-5 α -androstane-3-one was accomplished by sequential treatment with phenylselenenyl chloride in ethyl acetate and hydrogen peroxide. Elimination of phenylselenenic acid at room temperature gave the 1-en-3-one, which with alkaline hydrogen peroxide gave one of the 1,2-epoxy-3-ones, 18, stereospecifically. Reduction of the 1-en-3-one with sodium borohydride gave both stereoisomers of 19. These were epoxidized with *m*-chloroperbenzoic acid and subsequently oxidized with chromium trioxide-pyridine to generate both stereoisomers of 18. The stereochemistry of neither isomer of 18 could be assigned unequivocally from the ¹H NMR spectra; X-ray work will be utilized to settle these points. The more abundant isomer resulting from these experiments has been dehydrogenated with selenium dioxide in *tert*-butyl alcohol to give 14.¹⁴

The three epoxyenones thus obtained are similar and remarkably stable. They do undergo smooth aromatization under acidic conditions; 12 and 13 form the triacetate of 2 by the action of *p*-toluenesulfonic acid in acetic anhydride, and 14 yields, under similar conditions, the known triacetate of 3.⁸ On the other hand, the epoxyenones may be recovered unchanged from methanolic sodium methoxide (20 °C, 12 h) or potassium *tert*-butoxide-*tert*-butyl alcohol (20 °C, 12 h).

The synthesis of these tautomers of dienol epoxides derived from estradiol and their smooth aromatization suggest that they, in equilibrium with their dienol tautomers, may be intermediates in catechol estrogen biosynthesis. The aromatization step may be simply acid catalyzed or may be enzyme mediated.

Compounds 12-14 have been biologically evaluated in two ways. First, their activity on bacteriophage PM2 DNA, as measured by the creation of endonuclease-sensitive sites and subsequent agarose gel electrophoresis, was evaluated.¹⁵ The compounds were inactive by these criteria. Secondly, the compounds were subjected to the foci assay of Kakunaga,¹⁶ which involves determination of the chemical transformation of Balb/c 3T3 mouse fibroblast cells. From the 1-1A-10 line obtained from Dr. Takeo Kakunaga, a subclone (MN-20) was isolated which showed good contact inhibition, flat surface morphology, low spontaneous transformation frequency, and reproducible

transformation by 3-methylcholanthrene. Initial findings indicate, interestingly, that in this assay compound 13 (2 μ M) is approximately as active as the highly mutagenic 3-methylcholanthrene itself in inducing chemical transformation of the cells and at least two orders of magnitude more effective than estradiol. Compounds 12 and 14 were inactive at the same concentration as used for compound 13. Extensions of these chemical and biological experiments are in progress.

Acknowledgment. The work at Northeastern University was supported by the Office of Naval Research, Department of the Navy (Contract N00014-76-C-0027). The work at the Southwest Foundation was supported by Grant 1 R01 CA-24629-01 from the National Cancer Institute, DHEW. The original line of Balb/c 3T3 cells used in this work was kindly provided by Dr. Takeo Kakunaga, National Institutes of Health. The authors acknowledge the skillful technical assistance of T. J. Goodwin.

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Received May 11, 1979

Synthetic Modulators of the Complement System.

1. Synthesis and Biological Activity of 5,5',5''-[1,3,6-Naphthalenetriyltris(sulfonylimino)]-tris[1,3-benzenedisulfonic acid] Hexasodium Salt

Sir:

Considerable progress has been made in defining the constituents of the complement system and elaborating their role in the lysis of cells and the inflammatory process.¹ In addition, complement has been implicated in the pathophysiology of a number of diseases, e.g., rheumatoid arthritis, lupus erythematosus, glomerulonephritis and periodontitis.²

A possible approach to the treatment of complement-dependent diseases involves the use of a synthetic chemical modulator (activator or inhibitor) to assist the body's

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- (12) Cf. Hanson, J. R.; Wilkins, H. J. *J. Chem. Soc., Perkin Trans. I* 1974, 1388.
- (13) Compound 13 had mp 143-144 °C; [α]_D (EtOH) -55°; IR (film) ν_{\max} 3050, 1730, 1675, 1250, 1045, 1020 cm⁻¹; ¹H NMR (CDCl₃) δ 0.87 (3 H, s, C-18 Me), 2.03 (acetoxymethyl), 3.3 (1 H, d, *J* = 2 Hz, 4-H), 4.67 (1 H, br t, 17-H), 5.93 (1 H, d, *J* = 10 and 2 Hz, 2-H), 6.70 (1 H dd, *J* = 10 and 2 Hz, 1-H).
- (14) Compound 14 had mp 180-182 °C; [α]_D (EtOH) +149.6°; IR (film) ν_{\max} 3020, 1725, 1670, 1620, 1250, 1045, 1025 cm⁻¹; ¹H NMR (CDCl₃) δ 0.90 (3 H, s, C-18 Me), 2.03 (3 H, acetoxymethyl), 3.37 (1 H, dd, *J* = 4 and 2 Hz, 1-H), 3.70 (1 H, m, 2-H), 4.63 (1 H, br t, 17-H), 5.73 (1 H, br s, 4-H).
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