STUDIES IN THE SYNTHESIS AND BIOLOGICAL ACTIVITY OF A-RING STEROID DERIVATIVES

by

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A Thesis Submitted to the

Faculty of Graduate Studies and Research

of the University of Manitoba

In Partial Fulfillment of the Requirements

For the Degree Master of Science

March, 1978

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ACKNOWLEDGEMENTS

I would like to extend my sincerest gratitude to Dr. J. F. Templeton for his valuable criticisms, inexhaustable patience and assistance in preparing this dissertation. In particular, I would like to extend my appreciation to Dr. Templeton for his contribution in coherently presenting the biological section of this dissertation.

The assistance of Mrs. Donna Morris in preparing this manuscript is gratefully acknowledged.

Financial assistance from the Faculty of Pharmacy through Teaching Assistantships and Student Fellowships throughout this course of study is gratefully acknowledged.

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ABSTRACT

The isosteric and isoelectric relationships between the carbon-carbon double bond and the cyclopropane carbon-carbon bond of cyclic fusion of a variety of steroid derivatives are examined. These relationships may alter the biological activity and/or the biological potency of pharmacologically active steroid derivatives. The effect of the cyclopropane ring and the carbon-carbon double bond on the biological activity of pharmacologically active steroids is contrasted. Evidence suggests that the contribution of the cyclopropane ring and the carbon-carbon double bond to the biological activity of pharmacologically active steroids may be correlated, in part, to the contribution which these substituents make to the partition coefficient of the steroid molecule.

The preparation of 2α,3-dibromocyclopropano-5α-androstane-3β,17β-diol diacetate (94) from 5α-androst-2-ene-3,17β-diol diacetate (93) and dibromocarbene, prepared by the phase transfer technique, is described. Reduction of the dibromide (94) with the Zn/Cu couple and/or Raney nickel gave, exclusively, the monobromide 2α,3-(endo)-bromocyclopropano-5α-androstane-3β,17β-diol diacetate (97). Attempts to effect

complete dehalogenation utilizing a variety of other reductive procedures was unsuccessful in all cases.

The addition of the Simmons-Smith reagent to the enol acetate 93 and 3-trimethysilyloxy-17β-acetoxy-5α-androst-2-ene (115) is described.

The proton magnetic spectra of the brominated cyclopropanosteroids 94 and 97 and other C-2 cyclopropanosteroid derivatives indicated that the cyclopropane ring demonstrates a shielding effect which appears to operate through large distances. The mass spectra of the brominated cyclopropanosteroids 94 and 97, and other C-2 cyclopropanosteroid derivatives showed, with few exceptions, similar fragmentation patterns.

The preparation of 3,3-deuterio-17β-hydroxy-5α-androstane-d_2 (125) and 17β-hydroxy-5α-androstane (126) is described. Similarly, the preparation of 2α,3α-cyclopropano-17β-hydroxy-5α-androstane (118) and 2α,3α-cyclopropano-2β-4,4-deuterio-17β-hydroxy-5α-androstane-d_3 (121) is described.

Androgenic/myotropic assays of 118 and 121 suggested that metabolic activation at C-2 and/or C-4 accounted for the enhanced biological activity of 118 relative to 121. Androgenic/myotropic assays of 125 and 126 indicated that factors other than metabolic activation (of the A-ring) may account for the enhanced biological activity of 125 relative to 126.

TABLE OF CONTENTS

Page

B. PROGESTINS Continued

Page

B. PROGESTINS Continued

Page

C. ANTI-ANDROGENS Continued

Page

Page

Page

Page

Page

III. EXPERIMENTAL

Page

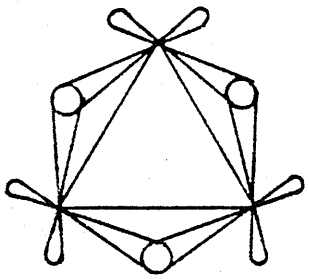
I. INTRODUCTION

A. THE CYCLOPROPANE RING

(i) The pseudo-unsaturated carbon-carbon bonds of the cyclopropane ring.

(a) Correlation with the carbon-carbon double bond.

The Coulson and Moffit model of the cyclopropane ring (Figure Ia) shows that the molecular orbitals which constitute the cyclopropane carbon-carbon bonds do not pass through the axis of the carbon atoms but are bent away from the axis of the carbon atoms (Figure Ib) by an angle of $22^{\circ}(\emptyset)$. Therefore, the angle between the carbon-carbon bonds of the cyclopropane fing ($\emptyset_1$) is 104° rather than $60^{\circ}(\emptyset_2)$. A 60° bond angle is the expected value if the molecular orbitals which constitute the bonds of the cyclopropane ring passed along the axis of the carbon atoms [1,2].



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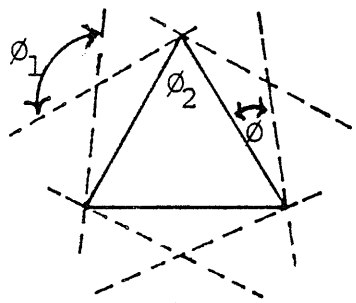


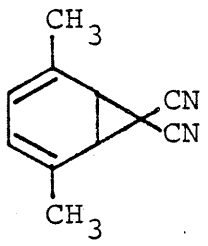
b

$\emptyset = 22^{\circ}$; $\emptyset_1 = 104^{\circ}$

$\emptyset_2 = 60^{\circ}$

Figure I. The Coulson and Moffit model of the molecular orbitals of the cyclopropane ring.

Electron density X-ray diffraction studies confirm the "bent bond" concept for the cyclopropane ring[1]. For example, the molecular orbitals that constitute the carbon-carbon bonds of the substituted cyclohexadiene derivative I have been shown to be bent away from the axis of the carbon atoms by 20°, i.e. $\phi = 20^{\circ}$. Therefore, as these molecular orbitals are bent, they are strained. It has been shown that each carbon-carbon bond of the cyclopropane ring possesses 8.68 kcal/mole strain energy. This excess bond energy accounts for the high reactivity of the cyclopropane ring.



I

The bent carbon-carbon bonds of the cyclopropane ring do not permit perfect overlap of the s molecular orbitals. Therefore, a considerably large proportion of the molecular orbital picture for the cyclopropane carbon-carbon bond constitutes p molecular orbitals. Calculations obtained by valence bond perfect-pairing approximation and minimization of the bond energies indicate that the carbon-carbon bonds of the cyclopropane ring are in fact $sp^{4.12}$ hybridized[1,2] and the carbon-

hydrogen bonds are $sp^{2.28}$ hybridized. Therefore, the molecular orbitals that constitute the carbon-carbon bonds of the cyclopropane ring, bear resemblance to the molecular orbitals that constitute the carbon-carbon double bond (sp^2 hybridized).

(b) The symmetrically bent cyclopropane carbon-carbon bond.

The symmetrically bent carbon-carbon bond[2] of the cyclopropane ring is the bond that is most frequently encountered in cyclopropane substituted cyclic and polycyclic systems. The bent bond can be referred to as the Type I cyclopropane bond, Figure II.

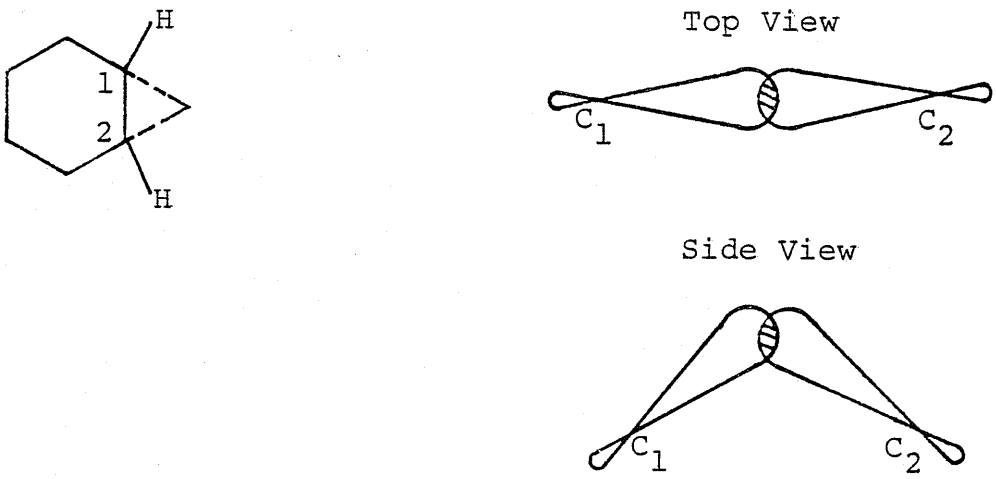


Figure II. Side and top view of the C-1(2) bond of a cis-substituted cyclopropane ring derivative.

(c) The non-symmetrically bent or twist bent cyclopropane carbon-carbon bond.

The twist bent cyclopropane carbon-carbon bond[2,3] represents a highly strained bond. The strain in these bicyclic structures arise from the inherent torquing which results when the cyclopropane ring is trans-fused to a cyclic molecule (Figure III). Twist bent, Type II, cyclopropane carbon-carbon bonds

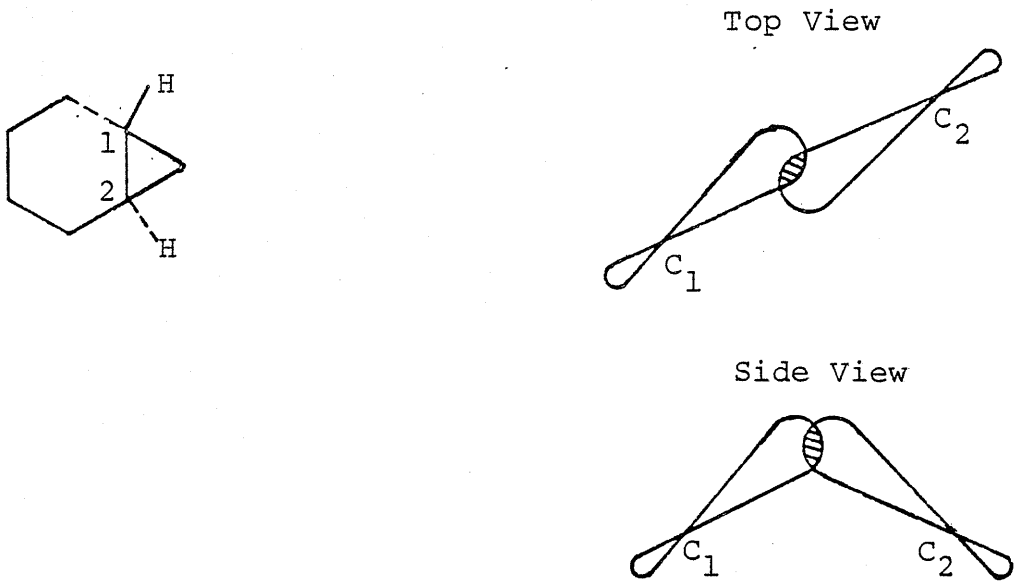


Figure III. Side and top view of the C-1(2) bond of a trans-substituted cyclopropane ring derivative.

demonstrate exceptionally high reactivity towards nucleophilic substances.[2] The polycyclic compound 2 and the bicyclic compound 3 are examples of substances demonstrating a Type II cyclopropane carbon-carbon bond [2,3].