of the Army Research Program on Malaria, was supported in large part by U.S. Army Medical Research and Development Command, Office of the Surgeon General, Contract No. DA-48-193-MD-2955, R. E. Lutz, Responsible Investigator, and in smaller parts by grants to the University of Virginia (R.E.L.) from the National Science Foundation (No. 8631) and A. H. Robins Co., Richmond, Va. Antimalarial and phototoxicity test data were supplied by Walter Reed Army Institute for Research. The test sample of 2-(*p*-chlorostyryl)amino alcohol **3** was prepared by D. A. Shamblee at Robins Co., Richmond, Va., working under S. J. Gillespie, Virginia Institute for Scientific Research, Richmond, Va. (Dec 1974). Work done independently and unpublished is here reported: (a) synthesis of **27** and a second synthesis of **2** by B. B. Corson, J. Pociask, H. C. Koppel, and J. Riedmaier, Aldrich Chemical Co., Milwaukee, Wis. (under support from WRAIR); and (b) synthesis of **36** and **37** by R. G. Bass and R. R. Hirjibehdin, Virginia Commonwealth University, Richmond, Va.

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# Conformational Influence of a 19-Methyl Substituent in 19-Oxygenated Steroid Structures

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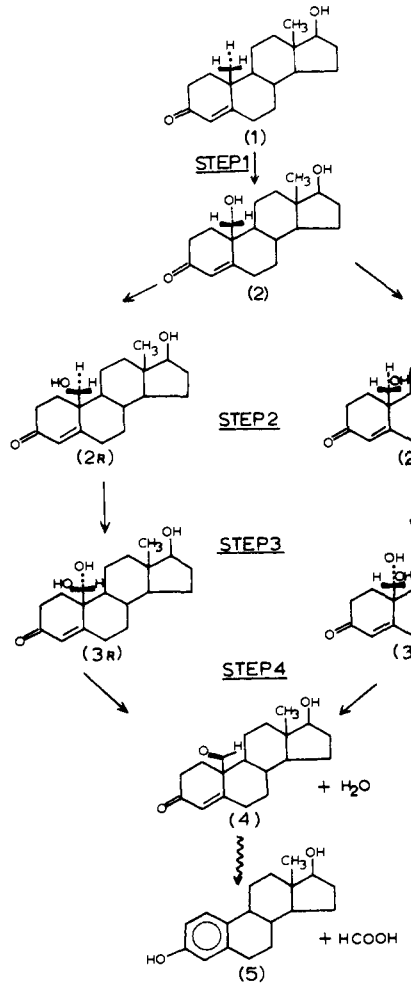
The crystal and molecular structure of (19*R*)-19-methyl-5-androstene-3$\beta$,17$\beta$,19-triol ($C_{20}H_{32}O_3$) has been determined. The crystals are orthorhombic and the space group is $P2_12_12_1$. The unit cell parameters are $a$ = 11.179 Å, $b$ = 21.485 Å, and $c$ = 7.328 Å. The structure was solved using the direct methods program MULTAN and refined anisotropically to an $R$ of 7.2% for all data. The methyl substituent on C(19) is located over the B ring and the hydroxyl between the A and C rings. The flexible B ring has a distorted half-chair conformation. The 19*R* configuration suggests that the reaction mechanism for the formation of this compound proposed by Wicha and Caspi is incorrect. Furthermore, these results indicate that the stereochemical assignment of C(19) by Skinner and Akhtar resulting from a tritiated sodium borohydride reduction is also suspect.

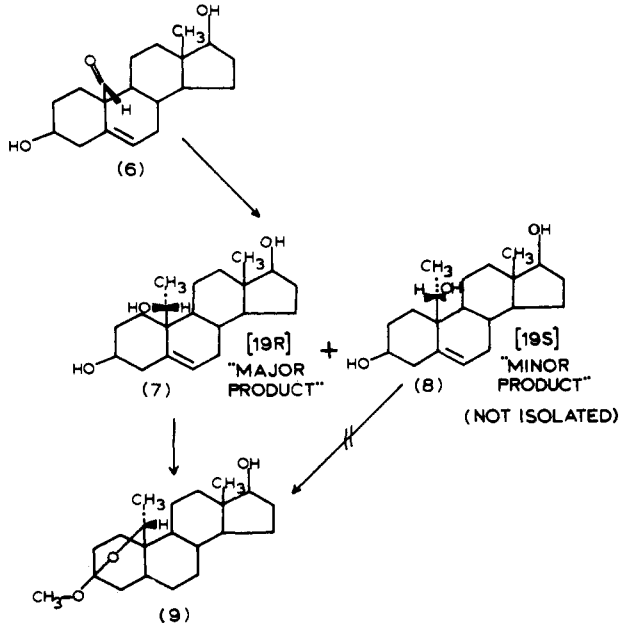
Chemical evidence combined with analysis of structural models or crystal structure data has led to two proposed mechanisms for the conversion of androgens to estrogens by the reaction of human placental microsomal aromatase.[1] These two mechanisms are very similar in many respects with the enzyme selectively attacking the hydrogen in the syn–anti–syn position, relative to C(1), C(5), and C(9), respectively, replacing it with a hydroxyl group (see Scheme I, step 1). The second step involves a rotation about the C(10)–C(19) bond followed by the enzymatic attack on one of the two remaining hydrogens (steps 2 and 3). Here, the two mechanisms differ. Skinner and Akhtar using tentatively assigned (19*R*)- and (19*S*)-$^3$H-19-hydroxyl substrate have postulated a 19-pro-*S* hydrogen ($H_S$) replacement, compound **2S**. Osawa using x-ray crystal structure data has assigned the opposite stereochemistry (**2R**) to the labeled substrate and proposed a 19-pro-*R* hydrogen ($H_R$) replacement. The latter requires the 19-hydroxyl to occupy the syn–syn–anti position over the A ring which is less sterically hindered than the anti–syn–syn position. The remaining steps in the mechanism are essentially the same.

The stereochemical assignments made by Skinner and Akhtar are based directly on previous work done by Caspi and Wicha.[2] The reaction sequence used by Caspi and Wicha (Scheme II) resulted in the formation of a methylated C(19) derivative **7**, but the stereoselective nature of the reaction should be the same as the reaction scheme used later by Skinner and Akhtar. The assignment of an *R* configuration to compound **7** was based on three ob-

Scheme I. Alternate Enzymic Reaction Mechanisms for the Conversion of Androgens to Estrogens by Human Placental Microsomal Aromatase as Proposed by Osawa[2] and Skinner and Akhtar[1]




Scheme II. Schematical Representation of the 19-Oxygenated Steroids Involved in the Reaction Sequence of Wicha and Caspi[3-5] for the Methyllithium Reduction and the Stereochemical Assignment of C(19)




servations. (1) Inspection of models seemed to indicate that rotation around the C(10)–C(19) bond was severely restricted and as a result the C(19) substituents should remain in a fixed conformation. (2) The methyl substituent must occupy the syn–anti–syn conformational position relative to C(1), C(5), and C(9) in order to minimize the energy resulting from intramolecular steric interactions. (3) The formation of a cyclic ether derivative, **9**, from the 19-hydroxyl to C(3) in the A ring required the 19-hydroxyl to occupy the syn–syn–anti position.

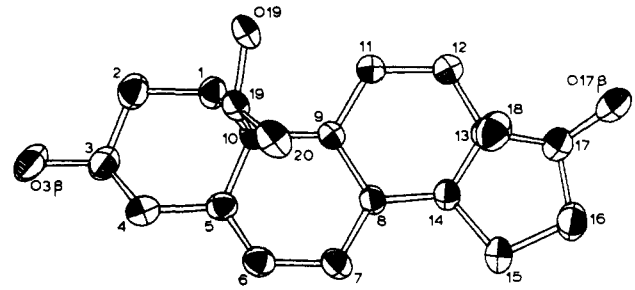



Figure 1. ORTEP[7] perspective view of (19*R*)-19-methyl-5-androstene-3β,17β,19-triol using 50% probability thermal vibrational ellipsoids.

In an effort to resolve the conflict between the two reaction mechanisms and to obtain further information about the conformational characteristics of 19-oxygenated steroids, the crystal and molecular structure of the minor product, **8**, in the reaction sequence of Caspi and Wicha has been determined.

## Experimental Section

**(19*R*)-19-Methyl-5-androstene-3β,17β,19-triol (8)** was synthesized via the reaction sequence described by Caspi and Wicha as a minor product. Recrystallization from acetone yielded crystals suitable for x-ray crystallographic investigation. A crystal with dimensions 0.4 × 0.3 × 0.4 mm was selected and used for data collection. The crystals are orthorhombic with systematic absences along each of the axial rows consistent with the space group $P2_12_12_1$ ($D_2^4$, no. 19). The lattice parameters were determined to be $a$ = 11.179 (6), $b$ = 21.485 (4), and $c$ = 7.328 (3) Å from a least-squares analysis of the $2\theta$ values of 29 reflections having magnitude greater than 55°. Intensity data were measured on a manually operated GE XRD-5 diffractometer by the stationary-counter, stationary-crystal technique using nickel-filtered Cu K$\alpha$ radiation and balanced cobalt filters to a maximum $2\theta$ of 140°. Using a criteria for observation of three estimated standard deviations, 1852 data were considered observed out of the 1941 data collected. After applying Lorentz and polarization corrections, normalized structure-factor amplitudes were computed and used in the automatic structure solution program MULTAN[3] to determine the structure.

The structural parameters were refined first isotropically and then anisotropically using a block-diagonal least-squares procedure. Fixed theoretically expected positions and isotropic $B$ values of 3.0 Å$^2$ were included in the final stages of refinement for 29 hydrogen positions and only those reflections with $|F_c|/|F_o|$ greater than 0.5 were allowed to influence the refinement. Weighting factors were calculated such that $w\Delta F^2$ were nearly independent of $|F_o|$ using the formula

$$w = [[1 + [(|F_o| - 12.0)/15.0]]^2]^{-1}$$

The final $R$ ($=\Sigma(||F_o| - |F_c||/\Sigma|F_o|$) factors for all of the data including the unobserved reflections and the observed data only were 7.2 and 7.0%, respectively. The final refined and theoretical atomic positions together with the anisotropic thermal parameters are given in Tables I and II.

## Discussion

The crystallographically determined molecular structure of (19*R*)-19-methyl-5-androstene-3β,17β,19-triol is shown in Figure 1. The bond lengths and angles shown in Figures 2a and 2b are all within the range of values found in other steroid molecules of this type and have estimated standard deviations in the ranges 0.007–0.008 Å and 0.3–0.4°, re-

Table I. Positional and Thermal Parameters[a] of the Nonhydrogen Atoms

| | X/A | Y/B | Z/C | U11 | U22 | U33 | U12 | U13 | U23 |
|---|---|---|---|---|---|---|---|---|---|
| C( 1) | 0.5363(3) | 0.8436(1) | 0.4295(5) | 0.0413(21) | 0.0295(17) | 0.0365(20) | -0.0018(17) | -0.0025(19) | -0.0033(17) |
| C( 2) | 0.5791(4) | 0.7763(1) | 0.4590(6) | 0.0535(26) | 0.0345(20) | 0.0497(26) | 0.0015(20) | -0.0030(25) | -0.0042(21) |
| C( 3) | 0.7118(4) | 0.7746(1) | 0.5047(6) | 0.0476(24) | 0.0325(18) | 0.0521(26) | 0.0051(18) | 0.0068(22) | 0.0050(20) |
| C( 4) | 0.7456(4) | 0.8197(1) | 0.6556(6) | 0.0392(22) | 0.0402(21) | 0.0523(26) | 0.0068(19) | -0.0027(22) | 0.0014(21) |
| C( 5) | 0.6940(3) | 0.8843(1) | 0.6284(5) | 0.0341(20) | 0.0360(19) | 0.0309(20) | 0.0044(17) | -0.0054(18) | -0.0011(17) |
| C( 6) | 0.7660(3) | 0.9334(1) | 0.6163(5) | 0.0337(20) | 0.0411(20) | 0.0354(21) | -0.0004(17) | -0.0001(18) | 0.0035(18) |
| C( 7) | 0.7267(3) | 0.9991(1) | 0.5938(5) | 0.0309(23) | 0.0411(20) | 0.0399(23) | -0.0056(18) | 0.0007(19) | 0.0023(19) |
| C( 8) | 0.5926(3) | 1.0079(1) | 0.6286(5) | 0.0305(19) | 0.0270(16) | 0.0344(20) | -0.0034(15) | 0.0019(18) | -0.0003(16) |
| C( 9) | 0.5212(3) | 0.9547(1) | 0.5359(5) | 0.0310(19) | 0.0292(18) | 0.0398(22) | -0.0018(15) | -0.0069(19) | -0.0014(17) |
| C(10) | 0.5587(3) | 0.8873(1) | 0.5949(5) | 0.0328(19) | 0.0269(16) | 0.0335(20) | -0.0026(15) | -0.0023(17) | -0.0030(16) |
| C(11) | 0.3844(3) | 0.9659(1) | 0.5430(7) | 0.0363(22) | 0.0317(19) | 0.0780(33) | 0.0005(18) | -0.0174(25) | 0.0014(23) |
| C(12) | 0.3480(4) | 1.0314(1) | 0.4723(8) | 0.0401(24) | 0.0335(20) | 0.0888(38) | 0.0018(18) | -0.0188(27) | -0.0010(25) |
| C(13) | 0.4162(3) | 1.0815(1) | 0.5773(6) | 0.0367(21) | 0.0311(19) | 0.0509(25) | 0.0019(17) | -0.0018(22) | -0.0030(19) |
| C(14) | 0.5500(3) | 1.0697(1) | 0.5500(5) | 0.0367(20) | 0.0274(17) | 0.0343(20) | -0.0037(15) | -0.0008(19) | 0.0014(16) |
| C(15) | 0.6104(4) | 1.1304(1) | 0.6177(6) | 0.0489(25) | 0.0294(18) | 0.0543(26) | -0.0066(19) | -0.0004(23) | 0.0012(19) |
| C(16) | 0.5176(4) | 1.1817(1) | 0.5658(7) | 0.0556(26) | 0.0339(20) | 0.0590(27) | -0.0040(20) | 0.0024(25) | 0.0003(22) |
| C(17) | 0.4063(4) | 1.1470(1) | 0.4932(6) | 0.0466(23) | 0.0336(20) | 0.0549(27) | 0.0028(19) | 0.0006(23) | -0.0025(20) |
| C(18) | 0.3789(4) | 1.0841(2) | 0.7772(8) | 0.0591(30) | 0.0432(24) | 0.0716(34) | 0.0047(23) | 0.0228(30) | 0.0078(25) |
| C(19) | 0.4938(3) | 0.8605(1) | 0.7672(6) | 0.0311(19) | 0.0323(18) | 0.0429(22) | -0.0040(16) | -0.0006(19) | -0.0021(18) |
| C(20) | 0.5018(4) | 0.8998(2) | 0.9390(6) | 0.0489(26) | 0.0587(26) | 0.0354(23) | -0.0117(21) | 0.0004(23) | 0.0001(22) |
| O( 3β) | 0.7467(3) | 0.7127(1) | 0.5613(5) | 0.0613(19) | 0.0320(14) | 0.0733(22) | 0.0130(14) | 0.0126(20) | 0.0078(16) |
| O(17β) | 0.2960(2) | 1.1804(1) | 0.5298(5) | 0.0532(19) | 0.0370(14) | 0.0840(25) | 0.0146(14) | 0.0014(20) | -0.0008(18) |
| O(19) | 0.3692(2) | 0.8459(1) | 0.7296(4) | 0.0356(15) | 0.0400(14) | 0.0544(18) | -0.0115(13) | -0.0032(15) | -0.0022(14) |

[a] The thermal parameters are of the form $\exp[-2\pi^2(U_{11}h^2a^{*2} + 2U_{12}hka^*b^* + \ldots)]$.

Table II. Atomic Positional Parameters for the Theoretically Positioned Hydrogen Atoms

| | X/Z | Y/B | Z/C |
|---|---|---|---|
| H( 1A) | 0.582 | 0.862 | 0.312 |
| H( 1B) | 0.441 | 0.842 | 0.401 |
| H( 2A) | 0.564 | 0.749 | 0.334 |
| H( 2B) | 0.528 | 0.755 | 0.568 |
| H( 3A) | 0.761 | 0.787 | 0.384 |
| H( 4A) | 0.842 | 0.822 | 0.661 |
| H( 4B) | 0.713 | 0.801 | 0.784 |
| H( 6 ) | 0.861 | 0.925 | 0.622 |
| H( 7A) | 0.746 | 1.014 | 0.456 |
| H( 7B) | 0.775 | 1.027 | 0.689 |
| H( 8B) | 0.575 | 1.007 | 0.774 |
| H( 9A) | 0.543 | 0.957 | 0.393 |
| H(11A) | 0.341 | 0.930 | 0.462 |
| H(11B) | 0.355 | 0.961 | 0.683 |
| H(12A) | 0.372 | 1.035 | 0.327 |
| H(12B) | 0.254 | 1.038 | 0.486 |
| H(14A) | 0.565 | 1.067 | 0.404 |
| H(15A) | 0.694 | 1.138 | 0.549 |
| H(15B) | 0.624 | 1.129 | 0.763 |
| H(16A) | 0.553 | 1.212 | 0.462 |
| H(16B) | 0.493 | 1.209 | 0.685 |
| H(17A) | 0.416 | 1.141 | 0.347 |
| H(18A) | 0.401 | 1.041 | 0.841 |
| H(18B) | 0.427 | 1.122 | 0.842 |
| H(18C) | 0.284 | 1.092 | 0.796 |
| H(19 ) | 0.536 | 0.817 | 0.798 |
| H(20A) | 0.595 | 0.905 | 0.973 |
| H(20B) | 0.463 | 0.945 | 0.909 |
| H(20C) | 0.456 | 0.881 | 1.058 |

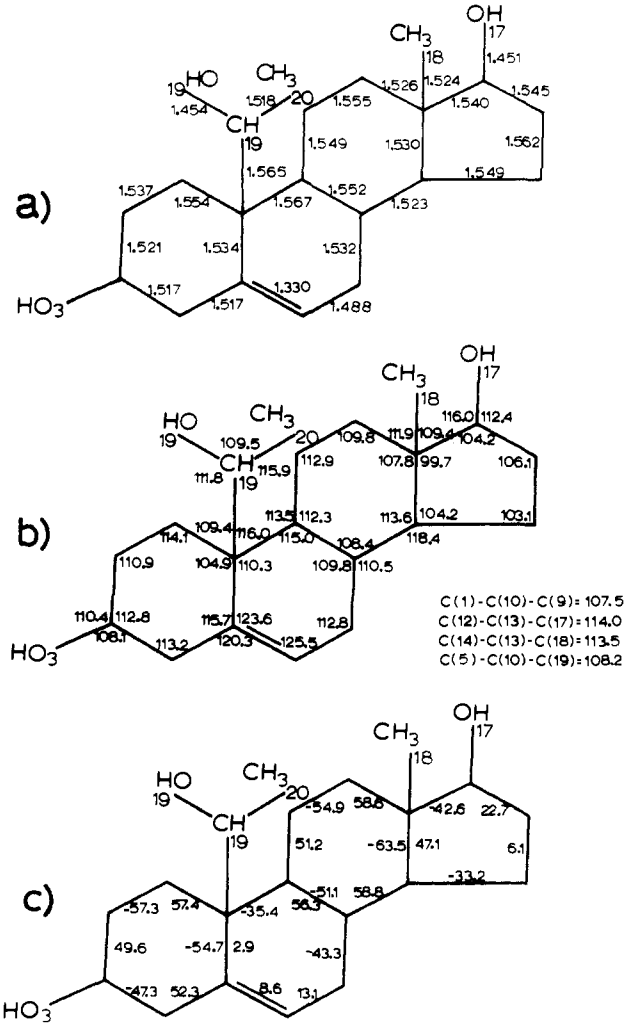



Figure 2. Observed bond lengths (a), bond angles (b), and intra-ring torsion angles (c) in (19*R*)-19-methyl-5-androstene-3β,17β,19-triol.

spectively. Figure 2c shows the intra-ring torsional angles in the steroid nucleus.

The absolute configuration of the C(19) is *R*, and the conformations of the 19-hydroxyl and 19-methyl substituents relative to C(1), C(5), and C(9) are syn–anti–syn and anti–syn–syn, respectively (see Figure 3). This is not only contrary to Caspi and Wicha's assignment of the absolute configuration of C(19) but also to their interpretation of the allowed conformation of C(20).

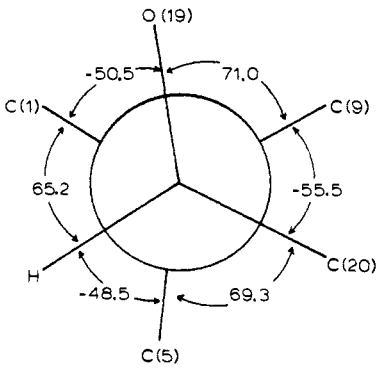



Figure 3. Newman projection viewed down the C(19) to C(10) bond showing the $R$ configuration and the relative positions of the C(19) substituents.

The conformations of the A and C rings are slightly distorted chairs with $\Delta C$ (chair) asymmetry parameters[4] of 5.6 and 6.4°, respectively. The distortion of the A-ring chair is a flattening of the ring in the C(3), C(4) region, as shown by the relatively small values of the C(2)–C(3) and C(3)–C(4) intra-ring torsional angles. The C-ring chair conformation has a combination of a slight flattening in the C(9), C(11) region and a puckering in the C(13), C(14) region.

The D ring is observed in a twisted C(13)$\beta$ envelope conformation with a pseudorotation in the direction of a C(13)$\beta$, C(14)$\alpha$ half-chair conformation. The pseudorotational parameters[5] are $\Delta = 20.3°$ and $\phi_m = 47.8°$.

The C(5)–C(6) double bond in the B ring allows a limited amount of conformational flexibility and in compound 8 the B ring has a conformation between an 8$\beta$, 9$\alpha$ half-chair and an 8$\beta$ sofa. This is indicated by the magnitudes of the $\Delta C_2$ [C(5)–C(10)] and $\Delta C_s$ [C(5)] asymmetry parameters for the B ring of 2.9 and 8.6°, respectively, and by the deviation of the C(8) and C(9) atoms from the least-squares plane calculated through atoms C(10), C(5), C(6), and C(7) of –0.47 and 0.23 Å, respectively.

In order to investigate the influence of the 19-methyl substituent of the flexible B ring, the crystal structures of nine comparable steroids[6] have been examined. The B ring in 8 is generally flattened with the average intra-ring dihedral angle being 26.6°. This is in contrast to an average value of 30.5° for the other structures examined. In particular, the C(10)–C(5)–C(6)–C(7) and C(9)–C(10)–C(5)–C(6) torsional angles in 8 are unusually large and small, respectively. The angular methyl valance angle C(9)–C(10)–C(19) is also much larger than the average value of 111.8° in the other ten structures.

A carbon atom was theoretically positioned on the angular methyl group, C(19), in each of these nine structures in the same orientation as that of compound 8 using the following parameters: bond length C(19)–C(20) of 1.518 Å, bond angle C(10)–C(19)–C(20) of 115.9°, and torsional angle C(1)–C(10)–C(19)–C(20) of –177.0°. The nonbonded contact distances between the B-ring atoms and the theoretically positioned carbon atom were calculated. A numerical value which can be used to evaluate the conformation of the B ring in these structures was obtained by calculating the difference between the $\Delta C_s$ [C(5)] and $\Delta C_s$ [C(6)] asymmetry parameters; the difference between these two parameters should be zero for an ideal half-chair conformation. A plot of the corresponding B ring to C(20) nonbonded contacts vs. conformation is given in Figure 4, and a linear least-squares fit was made for the corresponding points in each of the ten structures. Two of the resulting lines calculated for the C(5) and C(9) contacts have slopes less than two times

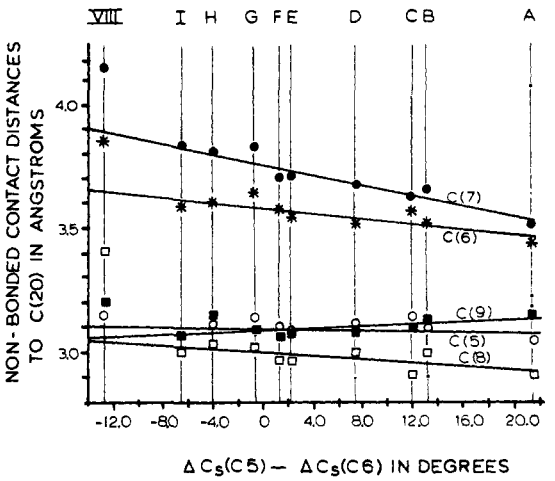



Figure 4. Graph of the B-ring conformational parameters vs. the B-ring atoms to theoretical C(20) nonbonded contact distances. Each line represents a least-squares fit of the corresponding B-ring atom contacts to C(20) for the crystal structures A–I. The slope and other comparative data are given in Table III. The crystal structures used are A, 16$\alpha$-iodo-3$\beta$-acetoxy-14$\alpha$,17$\alpha$-ethylene-5-pregnen-20-one, molecule 2;[6e] B, 3$\beta$-$p$-bromobenzoyloxy-13$\alpha$-androst-5-en-17-one;[6d] C, 3$\beta$-bromoacetoxy-16$\alpha$,17$\alpha$-[(1'$S$,-2'$S$)-1'$\beta$,2$\alpha$-dichloroethylene]-5-pregnen-20-one;[6f] D, 3$\beta$-chloro-5-androsten-17$\beta$-ol, molecule 2;[6a] E, 16$\alpha$,20-tetrafluoroethyleneoxy-5,17(20)-pregnadien-3$\beta$-yl $p$-bromobenzoate;[6g] F, 3$\beta$-$p$-bromobenzoyloxy-5-androsten-17-one;[6c] G, 3$\beta$-chloro-5-androsten-17$\beta$-ol, molecule 1;[6a] H, 16$\alpha$-iodo-3$\beta$-acetoxy-14$\alpha$,17$\alpha$-ethylene-5-pregnen-20-one, molecule 1;[6e] I, 17$\alpha$-iodo-5-androsten-3$\beta$-yl acetate.[6b]

Table III. Observed and Calculated Intramolecular Nonbonded Contact Distances (Å) between C(20) and the B-Ring Atoms in Compound 8

| B-Ring contact atom (A) | Slope of least-squares line[a] | C(20) to B-ring atoms for compd 8 | | |
|---|---|---|---|---|
| | | Obsd | Calcd[b] | Difference |
| C(5) | –0.001 (1) | 3.147 | 3.106 | 0.041 |
| C(6) | –0.006 (1) | 3.852 | 3.651 | 0.201 |
| C(7) | –0.011 (1) | 4.156 | 3.892 | 0.264 |
| C(8) | –0.003 (1) | 3.406 | 3.036 | 0.370 |
| C(9) | 0.002 (1) | 3.187 | 3.062 | 0.125 |

[a] The numbers in parentheses are the estimated standard deviation in the slope × $10^3$. [b] The calculated values were evaluated from the equation of the line at a [$\Delta C_s$ [C(5)] – $\Delta C_s$ [C(6)]] value of –12.8.

estimated error in the slope, which means there is no change in the nonbonded contact distance associated with the change in conformation. The other three lines for the C(6), C(7), and C(8) contacts all have slopes indicating a significant increase in the nonbonded contact distance as the conformation moves toward that observed for the 19-methylated structure, 8. However, in every case the extrapolated contact distances for the 19-methylated conformation are much less than the observed values for 8; see Table III. These observations indicate that the 19-methyl substituent has stabilized the flexible B ring in a conformation intermediate between a half-chair and a sofa in order to minimize the energy associated with the nonbonded interactions involving four of the six atoms in the B ring. In addition, the substitution has caused a flattening of the ring and an opening of the C(9)–C(10)–C(19) angle to further displace the methyl group away from the B-ring atoms.

There are only four intermolecular contacts between nonhydrogen atoms less than 3.48 Å. Three of these contacts result from what are presumably hydrogen bonds.

The hydrogen bonds between O(3) and O(19) and O(17) and O(19) are within the range normally observed, 2.828 and 2.926 Å, respectively. A third possible hydrogen bond involves O(3) and O(17) with a separation of 3.114 Å. The fourth short contact (3.318 Å) involves O(3) and C(18).

## Conclusions

These results also indicate that the conformation with the methyl group over the B ring should also be the preferred conformation in most solvents. Any change in the B-ring conformation or the conformation of the C-(19)-methyl substituent would result in shortening of the nonbonded contacts and a corresponding increase in energy.

The isolation of the 19*R* configuration as the minor product and conformation of the bulky C(19)-methyl substituent both indicate that the mechanism of Wicha and Caspi is incorrect. Furthermore, a 19*S* configuration for the major product[8] would require approach of C(19) by the methyllithium from over the less sterically hindered B ring. Since the mechanism of tritium addition and the configurational assignment of Skinner and Akhtar are dependent on the correctness of the methyllithium reaction, it also seems likely that these are also incorrect.

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**Supplementary Material Available:** listing of the structure factor amplitudes (9 pages). Ordering information is given on any current masthead page.

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# Contraceptive Agents from Cycloaddition Reactions of Diarylcyclopropenones and Diarylthiirene 1,1-Dioxides

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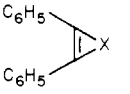
The potential for compounds with antifertility activity from the reactions of diphenylcyclopropenone (1) and 2,3-diphenylthiirene 1,1-dioxide (2) with enamines is described. In certain instances, a marked dissociation of antifertility from estrogenic activity was possible. Two series were studied extensively, one was stilbene amides (7) and the other stilbene amino ketones (8). The latter series (8) afforded several materials from which, on further biological work-up, was singled out compound 21 as a potent antifertility agent in rats and hamsters.

The synthesis of triarylethylenes,[1] diaryldihydronaphthalenes,[2] diarylindenes,[3] and diaryl heterocycles[4] and the antifertility activity of these compounds in rodents have been described.[5] Most of the compounds described have marked estrogenic or antiestrogenic activity. It was our intention to investigate compounds which were structurally very different from the above and whose antifertility activity was evident in doses far lower than those required to exert estrogenic activity. Some of the compounds screened in the present study did indeed demonstrate enhanced antifertility and reduced estrogenic activity.

At the beginning of this study, diphenylcyclopropenone (1)[6] and 2,3-diphenylthiirene 1,1-dioxide (2)[7] had been recently described and only the former had been utilized in cycloaddition reactions.[8] We recognized that these molecules contained a stilbene pharmacophoric group which could be incorporated into novel structures. We




1, X = C=O
2, X = $SO_2$

report here materials from such a study which exert marked antifertility activity in laboratory rodents.

**Chemistry.** The preparation of 1 and 2 and their derivatives (3, 4, and 5, respectively) was by literature methods (Table I).[6,9,10] Cycloadditions of 1 with acyclic and cyclic enamines were investigated (eq 1). Treatment of 1 with an equimolar amount of enamine according to ref 8 afforded their reported substance which the authors incorrectly assigned as 6 and a new substance whose analytical properties better fit this structural type. Further investigation showed the reported material in ref 8 to be amide 7 and the new substance, 6.[11] Certain structural