

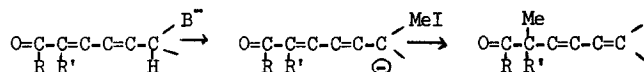
$\alpha$ -Methylation of Steroidal Dienones - The Total Synthesis of D,L-Androstenediones

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We wish to report the first example of  $\alpha$ -methylation of  $\alpha,\beta,\gamma,\delta$ -dienones via their  $\epsilon$ -anions. We do this in the context of the total synthesis of dl-androstenediones.



Treatment of I<sup>1</sup> with 1.2 eq of dimsyl sodium in DMSO followed by addition of excess methyl iodide gave a mixture from which was isolated a 12% yield of a monomethylated product, mp 134-135°,  $\lambda_{\text{max}}^{\text{EtOH}}$  244 m $\mu$ ,  $\epsilon=18,000$ . Its gross structure and stereochemistry were unambiguously established as II<sup>2</sup> by, three dimensional X-ray analysis (see discussion below and figure I).

Examination of the uncrystallizable portion (after recovery of 39% starting I) by infrared, ultraviolet and combined g.l.c.-mass spectrometry showed it to consist of small amounts of II, another monomethylated product, di- and tri-alkylated products and dehydrohalogenated versions of these. The  $\mu.v.$  spectrum ( $\lambda_{\text{max}}^{\text{EtOH}}$  244 m $\mu$ ) of this material indicated that these products as well as II contained the 8,14-diene chromophore. We reasoned that the monoalkylation reaction might be more successful if conducted on a substrate dienone containing a masked 17-ketone<sup>3</sup> and a side chain of greater base stability. Accordingly, trione III<sup>1</sup> was converted into diketalketone IV,<sup>2</sup> mp 86-87.6° in 70% yield.

Methylation of IV under the same conditions gave two monoalkylated products. These are assigned as V<sup>2</sup> (43% isolated yield, mp 108.5-109.5,  $\lambda_{\text{max}}^{\text{EtOH}}$  243 m $\mu$ ,  $\epsilon=20,000$ ) and VI,<sup>2</sup> (32% isolated yield, mp 87.5-88.5°,  $\lambda_{\text{max}}^{\text{EtOH}}$ ,  $\epsilon=23,000$ ) on the basis of correlation of the former<sup>4</sup> with products of unambiguous structure.

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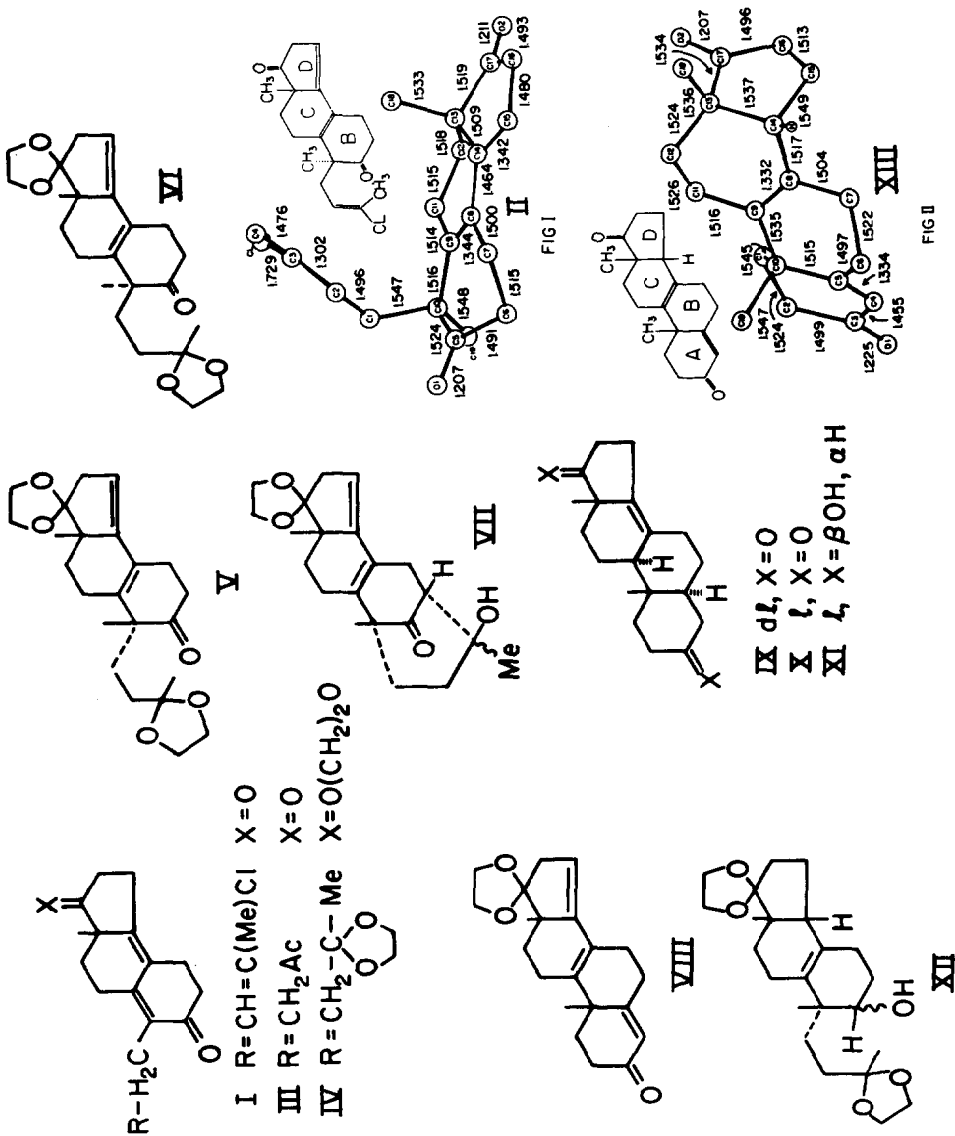
Treatment of V with dilute aqueous ethanolic acid at room temperature gave the bridged ketol VII<sup>2</sup> which was transformed (KOH-dioxane) into the tetracyclic ketaltrienone VIII<sup>2</sup> mp 133-134°. Further transformation of the latter via reduction (Li-NH<sub>3</sub>-EtOH), Jones oxidation and deketalization gave IX, mp 137-138°. That IX<sup>2</sup> is, in fact, dl-5 $\alpha$ -androst-8<sup>(14)</sup>-ene-3, 17-dione was established by the identity of its IR, nmr and mass spectra with those of the 1-form, X, <sup>2</sup> mp 149-150°, obtained via Jones oxidation of the known diol,<sup>5</sup> XI.

Treatment of V with lithium-ammonia-ethanol, gave in 66% yield, a tetrahydro product, XII mp 78-80°. Collins oxidation followed by double deketalization and cyclization (KOH-dioxene) gave dienedione, XIII,<sup>2</sup> mp 140.5-144° whose gross structure and stereochemistry were defined by three dimensional X-ray analysis (see discussion below and figure II). The contrast in the courses of chemical reduction of V (1,2-) and VIII (1,4-) are not, at present understood.

We now consider the three dimensional features of II and XIII. Both crystallize in the monoclinic space group P2<sub>1</sub>/C with four molecules per unit cell. The cell dimensions for II are<sup>6</sup>: A = 10.09 (3), b = 11.515 (3), c = 14.709 (4) Å;  $\beta$  = 92.54 (4)°. The structure was refined<sup>7</sup> to a reliability index<sup>8</sup>, R=0.081, for 2912 independent reflections. The near coplanarity of carbons 7, 8, 9, 10, 11, 13, 14, 15 and 16 is a distinctive feature of the molecule. The equation of the least squares plane through these atoms referred to the crystallographic axes is - 0.1662 x + 0.4082 y + 0.9041 z = 3.918. The methyl groups (C<sub>18</sub> and C<sub>19</sub>) are trans. C<sub>1</sub> of the chlorobutenyl side chain lies 1.239 Å above the least squares plane. C<sub>18</sub> extends 1.708 Å above the plane while C<sub>19</sub> projects 1.278 Å below the plane.

The cell constants for XIII are<sup>6</sup>: a = 7.388 (3), b = 18.641 (5), c = 12.432 (4) Å;  $\beta$  = 114.89 (4)°. The structure was refined<sup>7</sup> with anisotropic temperature factors to R = 0.06 for 2151<sup>8</sup> independent reflections. Rings B and C comprise an extended boat with carbons 6 and 12 puckered above the plane comprising carbons 5, 7, 8, 9, 10, 11, 13 and 14. Carbons 18 and 19 are cis and project above the BC ring plane by 0.623 and 1.340 Å, respectively. The CD rings are cis fused. Carbons 15, 16 and 17 lie 1.292, 2.328 and 1.541 Å, respectively, below the BC plane.

It is clear that the trigonal centers at carbons 5, 8 and 9 in structure II cause extensive flattening of the B ring and a complete disruption of the classical axial and equatorial



bonds. To the extent that the crystal structure may be used as a model for the extended enolate derived from IV, there emerges a ready interpretation for the loss of stereoelectronic control in this process.

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#### References

1. S. Danishefsky, L. S. Crawley, D. M. Solomon and P. Heggs, J. Amer. Chem. Soc., 93, 2356 (1971).
2. The structures of all new compounds are in accord with their infrared, nmr,  $\mu\nu$  and mass spectra. Combustion analyses within 0.3% of theory were obtained for the crystalline products.
3. It will be noted that compound II contains, potentially, a highly acidic proton at C<sub>16</sub>. This may be the reason for extensive polyalkylation.
4. A similar sequence of reactions has been conducted on VI and will be reported in a full paper.
5. R. Antonucci, S. Bernstein, D. Giancola and K. J. Sax, J. Org. Chem., 16, 1891 (1951).
6. Cell parameters and intensity data were measured by means of an automated diffractometer with CuK $\alpha$  radiation. Integrated intensities were collected by scanning the reflections in the  $\theta:2\theta$  mode.
7. Signs of the normalized structure factors were obtained by the direct method, and the atomic coordinates were taken from the associated E maps.
8.  $R = \sum |F_o| - |F_c| / \sum |F_o|$  where  $|F_o|$  and  $|F_c|$  are the observed and calculated structure factors respectively.
9. cf J. E. McMurry, Thesis, Columbia University (1967).