Tetrahedron Letters No. 3, pp 291 - 294, 1974. Pergamon Press. Printed in Great Britain.

# ADDITION OF DIMETHYLOXOSULFONIUM METHYLIDE TO STEROIDAL 4,6-DIEN-3-ONES: STERIC EFFECTS ON THE FORMATION OF THE 6,7-METHYLENE GROUP

G. E. Arth, G. F. Reynolds, G. H. Rasmusson, A. Chen and A. A. Patchett

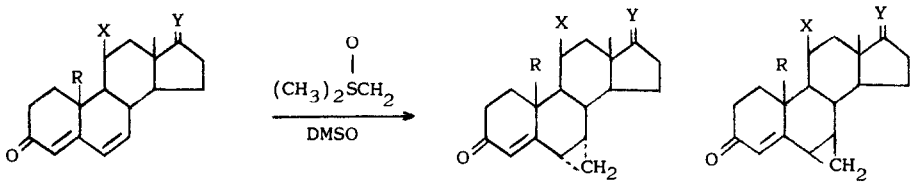
Merck Sharp & Dohme Research Laboratories
Rahway, New Jersey 07065

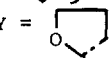
(Received in USA 28 September 1973; received in UK for publication 10 December 1973)

The reagent dimethyloxosulfonium methylide (DMSM) has frequently been used in steroid chemistry to convert α,β-unsaturated carbonyl systems to the corresponding cyclopropyl ketones.[1] The stereochemistry of the introduced methylene group has generally been that which would be predicted by preferred axial attack of the ylide from the least hindered side of the molecule. The orientation of addition to steroid cyclohexenenones and cyclopentenones with this reagent thus corresponds to that seen in the conjugate addition of the Michael reaction and of organometallic compounds.[1,2] It is not surprising that Dyson et al[3] in their initial analysis of the methylenated products from reaction of DMSM with $\Delta^6$-testosterone acetate (3) assigned the predominate product as having 6,7α-substitution. Subsequent studies by those workers[4] and others[5] has resulted in a reversal of this assignment. The formation of β-substituted product to such an extent is difficult to rationalize based on the observed conjugate addition of other nucleophiles which are known to produce 7α-substituents as the major or exclusive products.[6]

We have had occasion to react DMSM with a series of steroidal 4,6-dien-3-ones. The results of our studies are shown in Fig. 1.[7] The product ratios were derived by use of vapor phase chromatography. Our results with $\Delta^6$-testosterone acetate (3) confirm those described by earlier workers.[4,5] The 11β-hydroxy compound 5 with DMSM gave a single isolable isomer. The assignment of β-stereochemistry for this addition product is based on the fact that the material showed a strong negative molecular

Fig. 1

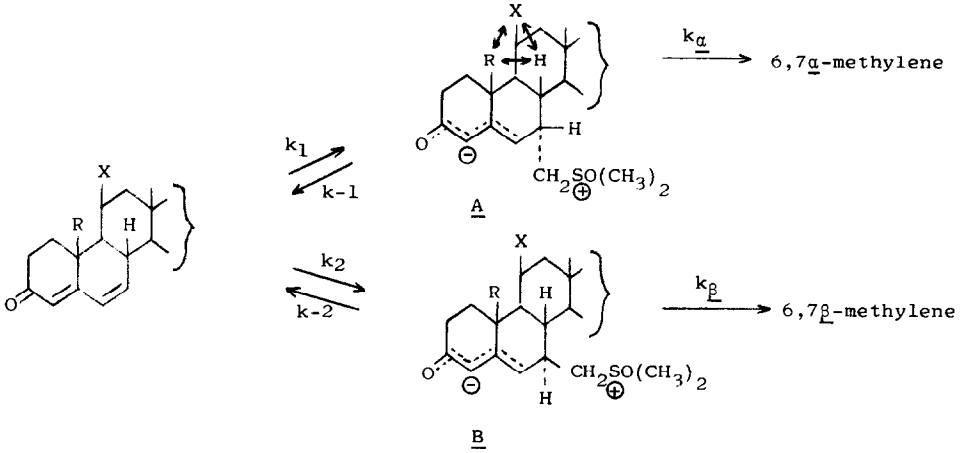



| Diene | Product Composition | $[M]_D$ | mp | $[M]_D$ | mp |
|---|---|---|---|---|---|
| 1 R = H; X = H; Y = β-OAc | α/β ≈ 90/10 | +313 | 166-169 | -407 | 139-141 |
| 2 R = H; X = H; Y =  | | +228 | 159-161 | -525 | 115-116 |
| 3 R = $CH_3$; X = H; Y = β-OAc | α/β ≈ 40/60 | +455 | 116-118 | -499 | 176-178 |
| 4 R = $CH_3$; X = H; Y =  | | +371 | 103-105 | -744 | 152-155 |
| 5 R = $CH_3$; X = β-OH; Y =  | α/β < 5/95 | -- | -- | -381 | 174-176 |
| 6 R = $CH_3$; X = O; Y =  | α/β ≈ 50/50 | -- | -- | -163 | 191-192 |

rotation shift $[M]_D$ characteristic of the other 6,7β-methylene adducts observed. The reaction of DMSM with a similar steroidal 11β-hydroxy-4,6-dien-3-one has been shown to give only β-adduct.[3,4] However, the 11-ketone 6 on reaction with DMSM gave an isomer mixture comparable to that of the 11-deoxy compounds 3 and 4. The assignment of stereochemistry to the methylene adducts of 4 was confirmed by reductive opening[8] of the cyclopropane ring to give the corresponding 7-methyl compounds. The reaction of methyl cuprate with the diene 4 gave the authentic 7α-methyl derivative, identical with that obtained from the minor component. Most surprising to us was the predominance of the α-methylene product in the reaction of the 19-norcompounds of 1 and 2 with DMSM.[11] The assignment of stereochemistry was based on $[M]_D$ changes and the reductive opening[8] of the cyclopropane ring of the major product derived from 2 to give a 7α-methyl compound. Authentic 7α-methyl compound was prepared in a multi-step sequence[9] from the methyl cuprate addition product of 4.

It is obvious that the reaction products of DMSM with these dienones is not governed by steric approach control, as the β-face of 10β-methylated steroids is generally regarded as being the more hindered side. One also might invoke van der Waals' attractive forces of the 10β-methyl group as enhancing the amount of 6,7β-methylene product formed. This is probably not the case as the qualitative rates of reaction of DMSM with this group of dienones are 1 & 2>3, 4, 6>5, indicating a rate retarding effect of 10β- and 11β-substitution. A more likely explanation is that the initial step of the addition of DMSM to the dienone system is reversible[10] and that axial (α) attack is preferred (see Fig. 2, $k_1 > k_2$). However, the formation of a cyclopropane in the subsequent step is subject to secondary steric interactions caused by torsional changes in forming the fused ring system. Thus, it would appear that ring closure to form α-methylene adducts with 10β-methyl (and even more with 10β-methyl-11β-hydroxy) compounds is inhibited by diaxial interaction involving the functions at the 8β, 10β and 11β positions. This type of interaction in formation of the β-methylene group is apparently not as serious, thus $k_\beta > k_\alpha$. In the case of 19-nordienones 1 and 2 these interactions are minimized (i.e., $k_\alpha$ R = H > $k_\alpha$ = $CH_3$) and the product is governed more by the concentration of the more rapidly formed α-intermediate (A).

Figure 2



## References


(1) H. Laurent and R. Wiechert in "Organic Reactions in Steroid Chemistry," Vol. II, J. H. Fried and J. A. Edwards, Eds. Van Nostrand Reinhold Company, New York, N. Y. 1972, Chapter 10.

(2) For a dicussion and references of conjugate additions to steroidal α,β-unsaturated ketones see: D. N. Kirk and M. P. Hartshorn, "Steroid Reaction Mechanisms," Elsevier Publishing Company, New York, N. Y. 1968, p. 192ff.

(3) N. H. Dyson, J. A. Edwards and J. H. Fried, Tetrahedron Letters, 1841 (1966).

(4) G. Tarzia, N. H. Dyson, I. T. Harrison, J. A. Edwards and J. H. Fried, Steroids 9, 387 (1967).

(5) J. Pfister, H. Wehrli and K. Schaffner, Helv. Chim. Acta, 50, 166 (1967).

(6) For example see: J. A. Campbell, and J. C. Babcock, J. Am. Chem. Soc., 81, 4069 (1959); G. C. Buzby, Jr., C. R. Walk and H. Smith, J. Med. Chem., 9, 782 (1966); R. G. Christiansen and W. S. Johnson, Steroids, 1, 620 (1963); W. Nagata, M. Yoshioka and M. Murakami, J. Am. Chem. Soc., 94, 4654 (1972).

(7) These reactions were run at room temperature in DMSO with the concentrations of excess (2-10-fold) DMSM at 0.2 to 0.8M depending on the rate of methylene addition. The product cyclopropylsteroids were relatively stable to the reagent and could be isolated unchanged in >75% yield when recycled through the conditions of the reaction. The reaction products of DMSM with 1, 2, 4 and 5 have been isolated, separated and characterized by spectral and combustion analyses. The products of the reaction of 6 with DMSM have not been separated but their isomeric relationship has been established by combination GC-MS analysis and by oxidation of the product from 5. A full paper describing the chemistry and the interesting biological properties of the compounds described in this communication is in preparation.

(8) The α-methylene derivative derived from 4 was opened with zinc in acetic acid[5] while the β-isomer from 4 and the α-isomer from 2 required a two-stage reduction, first opening with hydroiodic acid and then reductive removal of the iodide with zinc in acetic acid: H. Hofmeister, G. Schulz and R. Wiechert, Chem. Ber. 102, 2565 (1969).

(9) P. Wieland and G. Anner, Helv. Chim. Acta, 50, 289 (1967).

(10) It has been suggested that the related reagent (dimethylamino) phenyloxosulfonium methylide reacts reversibly with a methylene acceptor, see C. R. Johnson, M. Haake and C. W. Schrock, J. Am. Chem. Soc., 92, 6594 (1970).

(11) K. G. Holden and J. F. Kerwin, U. S. Patent 3,462,465 (1969) report the reaction of DMSM with 1 to give a mixture of the indicated methylene derivatives but an analysis of the mixture or the properties of the products were not described.