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STEROIDS CCXCIX.[1] THE METHYLENATION OF UNSATURATED KETONES PART III. THE ADDITION OF DIMETHYLOXOSULPHONIUM METHLIDE TO LINEAR CONJUGATED DIENONES.

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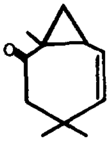
The methylene transfer reaction of dimethyloxosulphonium methylide with enones to yield cyclopropyl ketones is well established;(3,4) however, only in the case of eucarvone has this reagent been reported(3) to react with a conjugated dienone, to furnish the α,β-cyclopropyl enone (I).

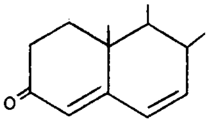


I

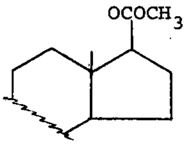
The first examples are now reported of the reaction of this ylid with linear conjugated dienones to give predominantly the γ,δ-cyclopropyl-α,β-unsaturated ketones. The reaction, using 1-2 equivalents of the ylid in dimethyl sulphoxide at room temperature, proceeds slowly and requires 2-3 days for completion in contrast to eucarvone, where cyclopropane formation is complete in less than 3 hours.

Reaction of 17β-hydroxyandrosta-4,6-dien-3-one or its acetate (IIa) with dimethyloxosulphonium methylide gave a 54:46

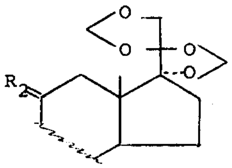
mixture(5) of 6α,7α- and 6β,7β-methylene adducts.(6) Fractional crystallization of the acetates afforded 17β-acetoxy-6α,7α-methylenandrost-4-en-3-one (IIIa) [m.p. 176-177.5°; $[\alpha]_D$ -171°;



II

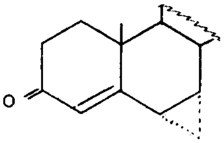


a

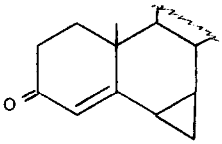


b $R_2 = H_2$

c R_2 = α-H, β-OH



III



IV

λ_{max} 263 mμ (ε 17,100); n.m.r. 49.5 (18-H), 65.5 (19-H), 361 c.p.s. (4-H). Found: C, 77.14; H, 8.76](7).

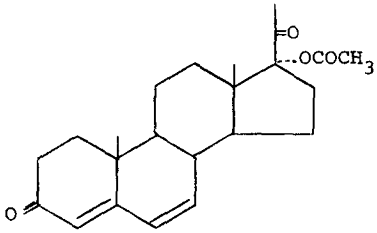
Similarly, reaction of 17α,20:20,21-bismethylenedioxypregna-4,6-dien-3-one (IIb) with dimethyloxosulphonium methylide gave a 57:43 mixture(5), which was not separable by crystallization, of 6α,7α- and 6β,7β- adducts (IIIb and IVb) [m.p. 202-208°; λ_{max} 263 mμ; n.m.r. 51, 54.5 (18-H in the α- and β- isomers), 65.5, 69 (19-H in the α- and β- isomers), 357.5, 360.5 c.p.s. (4-H in the β- and α- isomers respectively)].

The proportion of 6β,7β-adduct formed in the methylene transfer reaction is very susceptible to alteration by substitution at C-11 of the steroid nucleus. Thus, 17α,20:20,21-bismethylenedioxy-11β-hydroxypregna-4,6-dien-3-one (IIc) afforded

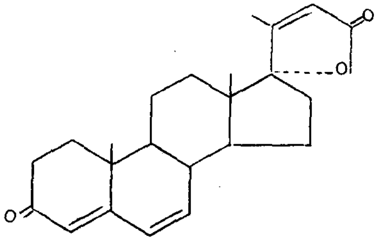
17α,20:20,21-bismethylenedioxy-11β-hydroxy-6α,7α-methylenepregn-4-en-3-one (IIIc) [m.p. 233.5-235°; $[\alpha]_D$ -160°; λ_{max} 266 mμ (ε 18,500); n.m.r. 67.5 (18-H), 80.0 (19-H), 356 c.p.s. (4-H). Found: C, 68.91; H, 7.85] with no detectable trace of the 6β, 7β- isomer (IVc).

The stereochemistry of IIIc would be expected to be alpha since appreciably greater steric and electrostatic non-bonding interactions arise by approach of the reagent to the β-face(8) of IIc, as compared to approach to the α-face. Comparison of the 19-H resonance of IIIc with 17α,20:20,21-bismethylenedioxy-11β-hydroxypregn-4-en-3-one indicates a shielding effect of about 8 c.p.s. for the newly introduced 6α,7α-cyclopropyl group.(9) Thus, the shielding of about 7 c.p.s. found with IIIa and IIIb suggests the α-stereochemistry for these adducts, whereas the shielding of about 3.5 c.p.s. on the 19-H resonance of the respective 6,7-unsubstituted-4-en-3-ones observed with IVa and IVb suggests the isomeric β-stereochemistry.

In contrast to these examples 17α-acetoxypregna-4,6-diene-3,20-dione (V) reacts rapidly (less than 1 hour) with dimethyloxosulphonium methylide in dimethyl sulphoxide to give 17α-hydroxy-3-oxo-23-norchola-4,6,20(22)-trienoic acid lactone (VI) [m.p. 227-228.5°; $[\alpha]_D$ -191°; λ_{max} 216 (ε 13,300), 282 mμ (ε 23,500); ν_{max} 1749, 1670, 1621, 1590 cm^{-1}; n.m.r. 61.5 (18-H), 67.5 (19-H), 130 (doublet, J = 0.6 c.p.s., 21-H), 341 (4-H), broad singlet at 351 (22-H), 369 c.p.s. (6-H and 7-H). Found: C, 77.85; H, 8.05; molecular ion 352]; which is very probably formed by an intramolecular aldol-type reaction and subsequent dehydration.(10)



V



VI

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2. Syntex Postdoctoral Fellow 1964-1965.

3. E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1353 (1965) and previous communications cited therein.

4. H-G. Lehmann, H. Muller and R. Wiechert, *Chem. Ber.*, **98**, 1470 (1965).

5. The proportion of isomers was determined by vapor phase chromatography. We wish to thank Dr. L. Throop and his associates for the physical constants and vapor phase chromatographic data reported herein.

6. No effort was made to optimize the yields which ranged from 32-62%.

7. Rotations are recorded in $CHCl_3$ (C 0.1).

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10. After this work had been completed a communication by H-G. Lehmann, *Angew. Chem. Intern. Ed. Eng.*, **4**, 783 (1965), appeared which demonstrates that this reaction is indeed a general one for tertiary α-acetoxy ketones.