Solvent Dependency of the Steric Course of Dienolate Alkylation

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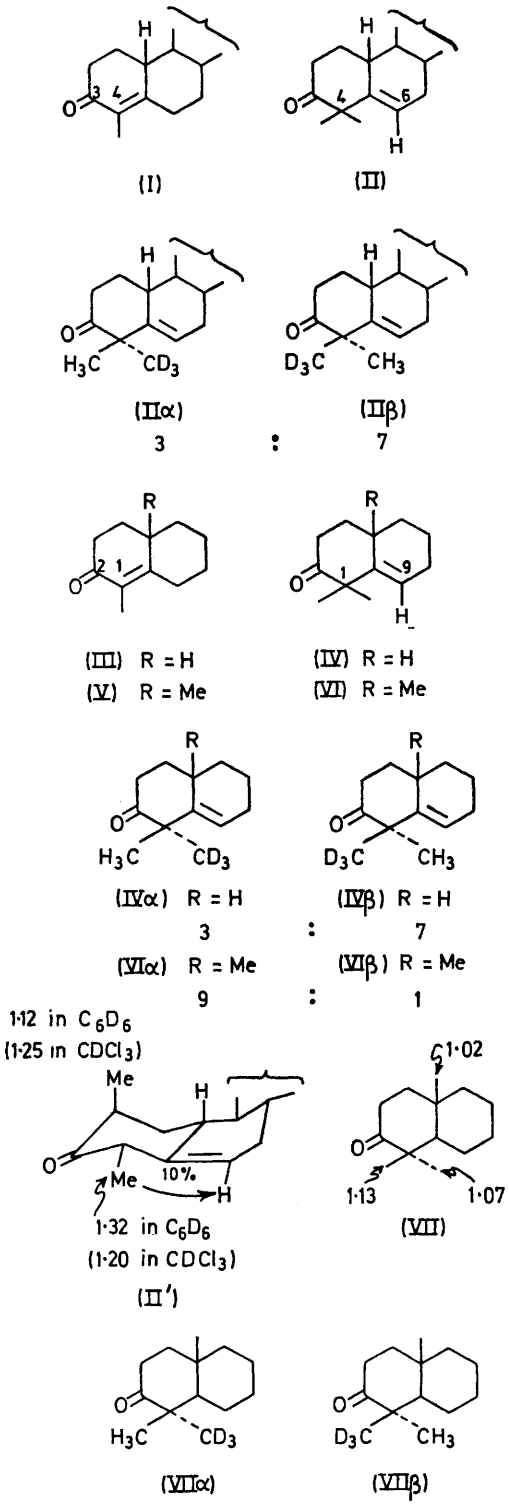
Summary The stereochemistry of methylation of α-methyl-αβ-unsaturated enones is shown to be dependent on reaction media.

WE present evidence that alkylation of dienolate anions derived from enones (I) and (II) are markedly affected by the solvent system, and that this factor should be considered seriously in alkylation reactions. The enolate anion of 17β-acetoxy-4-methyl-19-testosterone (I)[1] formed with $EtC(Me)_2OK$–C_6H_6 was treated with MeI to give, after acetylation, the 4,4-dimethyl steroid (II)[2] (52% overall yield); c.d. (EtOH) $\Delta\epsilon_{295}$ + 2·58; u.v. (EtOH) ϵ_{295} 90. The positive Cotton effect together with enhanced u.v. maximum (n,π^*) establishes a chair conformation for ring A.[3] N.m.r. signals of the 4,4-dimethyl group appear in $CDCl_3$ at 1·20 and 1·25 p.p.m. and are not sufficiently separated for



intramolecular nuclear Overhauser effect (N.O.E.) studies.[4] However, in C_6D_6 they are shifted to 1·12 and 1·32 p.p.m.; irradiation of the 1·32 p.p.m. signal caused a 10% increase in the integrated area of the olefinic 6-H signal at 5·51 p.p.m. No increment was observed upon irradiation of the 1·12 p.p.m. signal. The 1·32 and 1·12 p.p.m. signals can therefore be assigned unambiguously to the 4α- and 4β-methyl groups (see II′), respectively.

In order to study the steric factors involved in this reaction, the same dienolate alkylation was next carried out with CD_3I, which gave a mixture of (IIα) and (IIβ).† The intensity ratio of n.m.r. signals at 1·12 and 1·32 p.p.m. in C_6D_6 (1·25 and 1·20 p.p.m. in $CDCl_3$, respectively) (see II′) indicated that 4α-methylation giving (IIα) and 4β-methylation giving (IIβ) had occurred in a ratio of 3:7. Namely, a β-attack was favoured in benzene.

The conversion of (I) into (II) [and also to (IIα)/(IIβ)] had been carried out previously by treatment with Bu^tOK–Bu^tOH and then with MeI.[5] On the basis of n.m.r. intensity measurements of the deuteriated species (IIα)/(IIβ), it was concluded that this ratio was 1:10. However, assignments of the two methyl groups at 73 and 75 Hz (from Me_4Si, 60 MHz) were opposite‡ to those described above as derived from N.O.E. measurements. Accordingly, the previous conclusions[5] also have to be reversed, *i.e.*, in Bu^tOH an α-attack is preferred over β-attack to the extent of 10:1. This is contrary to the present results carried out in benzene, and shows that the solvent§ has a profound effect on the stereochemical course of enolate alkylations.

Similar alkylation of (±)-decalone (III) with EtC-$(Me)_2OK$–C_6H_6 and MeI gave the 1,1-dimethyl product (IV) in 55% yield; u.v. (EtOH) ϵ_{295} 100. Again, the 1·28 p.p.m. peak (in C_6D_6) exhibited a 15% N.O.E. on the 5·50 p.p.m. 9-H signal and thus could be assigned to the 1α-methyl group; the 1β-methyl appeared at 1·08 p.p.m. Alkylation with CD_3I yielded a mixture of (IVα) and (IVβ) in a ratio of 3:7 (1α- and 1β-methyl groups appeared at 1·21 and 1·26 p.p.m., respectively, in $CDCl_3$), which indicated that, as in the case of (I) → (II), a β-attack was predominant.

The effect of a 5-methyl substituent on the direction of alkylation in benzene was investigated next with the angularly substituted decalone (V). Dienolate alkylation under the present conditions gave (VI) in 80% yield; u.v. (EtOH) ϵ_{290} 33; n.m.r. ($CDCl_3$) 1·22, 1·22, 0·99 (three methyls); (C_6D_6) 1·27, 1·27, 0·91 p.p.m. Due to overlap of the n.m.r. methyl peaks in enone (VI), this was converted into the known saturated ketone (VII)[7] (and <10% of *cis*-isomer, as judged from n.m.r.) in practically quantitative yield, *via* (i) reduction with $LiAlH_4$, (ii) hydrogenation over Pd–C–EtOH, and (iii) Jones oxidation; the carbonyl-reduction step was carried out in order to ensure stereospecific hydrogenation.¶ This saturated ketone (VII) had been obtained through reductive methylation of (V) by Stork, *et al.*,[6] and the stereochemistry of the alkylating step has recently been clarified by Mathews, *et al.*[7,8] As the n.m.r. methyl peaks (in $CDCl_3$) had already been assigned as depicted in (VII),[7] it was possible to clarify the

† The physical constants of (II) and (IIIα)/(IIβ) were identical except for the appearance in the i.r. of the latter of C–D stretching bands at 2250, 2510, and 2070 cm^{-1}.

‡ The critical assignments of the peaks were erroneously based on the assumption that the chemical shift of a methyl in a 4,4-gem-dimethyl group would be the same as that of a methyl in a 4-methyl-4-ethyl group.

§ We have presumed that difference in solvent polarity exerts a larger effect than the reagent base.

¶ Direct hydrogenation of (VI) resulted in a *ca.* 1:1 mixture of *cis* and *trans* saturated ketones, which could not be separated under various t.l.c. conditions. However, in the three-step reaction, the *trans* isomer was formed predominantly (>90%).

steric preference of the $EtC(Me)_2OK$–C_6H_6–MeI alkylation reactions. Thus it was found that decalone (V) gave compounds (VIIα) and (VIIβ) in a 9:1 ratio with $EtC(Me)_2OK$–C_6H_6–CD_3I which meant that the major course was now an α-attack as expected.[9]

The results of alkylation carried out in the present non-polar benzene system, especially those of (I) and (III), can be rationalized on the basis of a product-like transition state (sp^3 configuration at alkylating site) rather than a dienolate-like transition state (sp^2). Specific solvation by Bu^tOH on the less hindered side (β) of the anion resulting in α attack of methyl is another possible explanation.

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