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STEREOSELECTIVITY IN ALKYLATION OF KETONES INDUCED BY POLAR SUBSTITUENTS.

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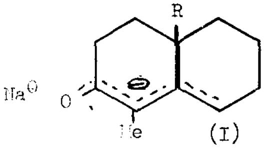
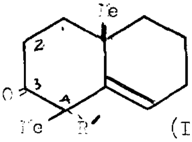
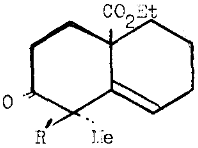
We have drawn attention (1) to a steric preference in alkylation of enols (I, R = CH_3 or CO_2Et) where the isomers (II) and (III) respectively form the major products of C-alkylation of (I, R = CH_3) and (I, R = CO_2Et) with benzyloxymethyl chloride. This difference we have attributed to steric repulsion favouring reaction on the side opposite to the alkyl group i.e. on the α-face of the molecule, and to a polar influence of the ester group potentiating reaction on the same side i.e. on the β-face of the molecule (1). We now report further results in which a cyano-group as in (I; R = CN) is also found to promote syn- i.e. β-alkylation as in (III). The relevent chemistry is summarised:



(I)

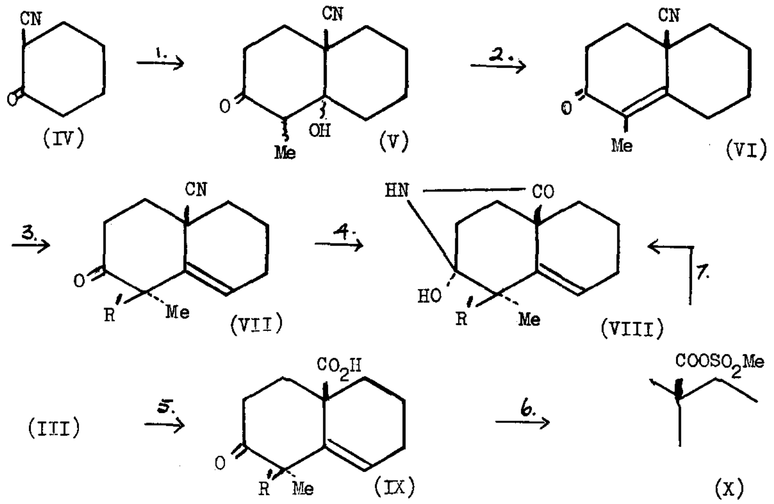


(II)



(III)

$R' = PhCH_2OCH_2$

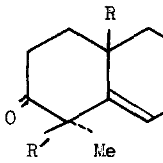


R' = $PhCH_2OCH_2$-

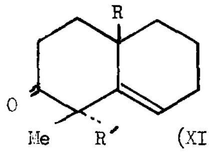
1. $EtCOCH_2CH_2\overset{+}{N}MeEt_2$, I^-+ NaOEt in benzene. 2. p-$MeC_6H_4SO_3H$ in benzene.
3. NaH/dioxan, then $PhCH_2OCH_2Cl$/dioxan. 4. NaOH/DMSO. 5. aq.alc. KOH.
6. $MeSO_2Cl/Et_3N/CH_2Cl_2$. 7. NH_3 gas.

The major alkylation product (VII), m.p. 55°, gave an N.M.R. signal due to the 4 Me- group as a singlet at 8.78 τ in deuterochloroform, moved to 8.69 τ in benzene (60 Mc., relative to TMS). This solvent shift (2) indicates a 4 α-orientation for the methyl group. This conclusion was confirmed chemically by inter-relating (VII), through the lactam (VIII), m.p. 105°, with (III), the stereochemistry of which has already been rigorously proved (1a). The formulation of (VIII) as the lactam rather than as a keto amide follows from the infrared absorption: 3590 (HO), 3390 (NH), and 1675 cm.$^{-1}$ (-CO-NH-), with no ketone carbonyl band, and from a number of precedents (3).

Isomeric products (XI) and (XII) may be distinguished (1b) as indicated by the N.M.R. signal of the 4 Me- group viz:



(XI)



(XII)

R′ = $PhCH_2OCH_2$-

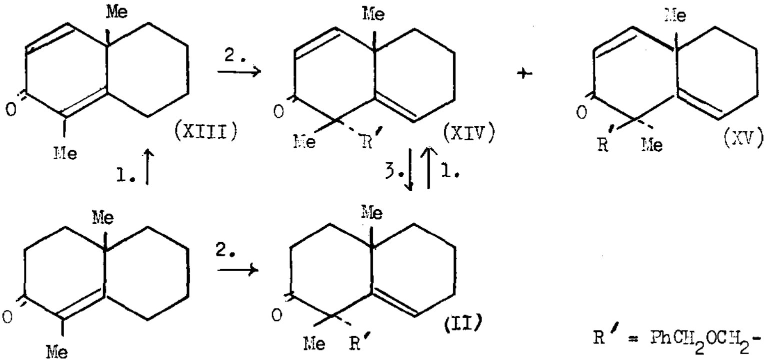
R = Me	4αMe: 8.74 τ	4βMe: 8.92 τ
R = CO_2H	8.68 τ	8.82 τ

The 4Me-signal of (VII) at 8.78 τ is in the lower i.e. 4α- range. We were unable to recognise any second methyl signal in the residue from crystallisation of (VII). The 4β-methyl isomer would therefore not appear to be formed in any large amount.

The groups R = Me, CO_2Et and CN differ considerably in steric volume; the group conformational energies (4) are indicative:

R :	Me	CO_2Et	CN
$-\Delta G°$:	1.7	1.1	0.15 k.cal./mol.

Reduced steric hindrance could therefore contribute to alkylation syn to the R-substituent in the case R = CO_2Et or CN. In an attempt to assess the importance of this factor we have examined the alkylation of (XIII) in which resistance to 4β-substitution should be reduced by the absent 2βH- : 4β interaction. Use of a dehydro-ketone has proved a useful device in other cases for reversing the steric preference in alkylation (5). The stereochemistry of the major C-alkylation product (XIV) was related with (II) as indicated. N.M.R. analysis of the reaction product showed: (XIV; 4Me τ 8.82) 57%, (XV; 4 Me τ 8.65)) 10%, and some 33% of O-alkyl product. Since (I, R = Me) gives (XI, R = Me) 59%, (XII, R = Me) 11%, and 30% O-alkyl product, the alkylation reaction does not appear to be unduly sensitive to the level of steric hindrance on the β-face of the molecule. The major influence of the CO_2Et- or CN- group may therefore safely be ascribed to polarity. Incidentally the closely comparable behavior of the enolate of the rigid structure (XIII), and of (I, R = Me) excludes reaction of (I) in a deformed or boat- type conformation.



R′ = $PhCH_2OCH_2$-

1. 2,3-Dichloro-5,6-dicyanoquinone/dioxan.
2. NaH/dioxan followed by $PhCH_2OCH_2Cl$.
3. H_2/Pd charcoal in alkaline ethyl alcohol.

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