Ambident Ion. IV. *C*-Alkylation of Enolate Anion Accompanying Retention of Configuration

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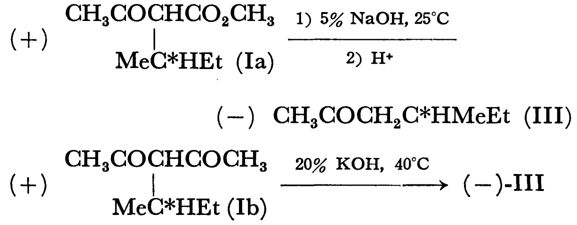
Recent report by Sommer and Korte[1] showed that charge-delocalized organolithium reagent coupled with optically active secondary halides with nearly complete inversion of configuration. According to Hart,[2] *C*-alkylation of phenoxide ion also proceeds with inversion of configuration. We wish to report our findings which are in sharp contrast to these results. Reaction of *sec*-butyl bromide with alkali metal salts of methyl acetoacetate and acetylacetone gives *C*- and *O*-alkylated products.[3]

$$(\mathrm{CH_3COCHCOR})^-\mathrm{M}^+ + sec\text{-}\mathrm{BuBr} \longrightarrow \underset{\text{(I)}}{\mathrm{CH_3COCH(Bu^s)COR}} + \underset{\text{(II)}}{\mathrm{CH_3C(OBu^s){=}CHCOR}} + \mathrm{MBr}$$

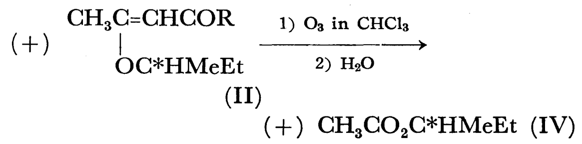
$$\mathrm{a{:}R{=}OMe} \quad \mathrm{b{:}R{=}Me}$$

Results with the optically active bromide in DMSO are given in Tables 1 and 2. Absolute configurations of optically active I and II, which are not known so far, have been determined in correlation with III and IV through the following reaction sequences:



$$(+)\ \underset{\text{MeC*HEt (Ia)}}{\underset{|}{\mathrm{CH_3COCHCO_2CH_3}}} \xrightarrow[\text{2) H}^+]{\text{1) 5\% NaOH, 25°C}} (-)\ \mathrm{CH_3COCH_2C^*HMeEt}\ \text{(III)}$$

$$(+)\ \underset{\text{MeC*HEt (Ib)}}{\underset{|}{\mathrm{CH_3COCHCOCH_3}}} \xrightarrow{\text{20\% KOH, 40°C}} (-)\text{-III}$$



$$(+)\ \underset{\text{OC*HMeEt}}{\underset{|}{\mathrm{CH_3C{=}CHCOR}}}\ \text{(II)} \xrightarrow[\text{2) H}_2\text{O}]{\text{1) O}_3\text{ in CHCl}_3} (+)\ \mathrm{CH_3CO_2C^*HMeEt}\ \text{(IV)}$$

It has been established that Ia and Ib have (−) R and IIa and IIb have (+) S structures.[4] The results show that *C*-alkylation proceeds with retention of configuration. The extents of the retention should be much higher (25—50%) than the observed values (Table 2), since control experiments showed that the starting active butyl bromide racemizes in the presence of metal halides which are formed by the reaction. This indicates that *C*-alkylation is not a simple S_N2 reaction by free carbanion species, and that some front-side attack to assymmetric center must have occurred. On the other hand, in the *O*-alkylation of sodium salts, taking the rate of racemization of the bromide into consideration, the results show almost complete inversion of configuration which suggests a typical S_N2 reaction of enolate anion (Table 2).

These stereochemical results show that *C*- and *O*-*sec*-butylations are not simple competitive reactions through a common transition state.[6] For a more detailed discussion, precise stereochemical and kinetical investigations are necessary.

Table 1. *sec*-Butylation of sodium and lithium enolates by optically active bromide in DMSO (50 g)

Exp.	Enolate	mmol	*sec*-Bu*Br mmol	Temp. °C	Time hr	Alkylates % I	Alkylates % II	Total Yield%
1	$(\mathrm{CH_3COCHCO_2CH_3})^-\mathrm{Na}^+$	20	19	60°	41	48	52	65
2	$(\mathrm{CH_3COCHCO_2CH_3})^-\mathrm{Na}^+$	31	31	50—55°	51	46	54	51
3	$(\mathrm{CH_3COCHCOCH_3})^-\mathrm{Na}^+$	20	19	60°	42	26	74	54
4	$(\mathrm{CH_3COCHCO_2C_2H_5})^-\mathrm{Li}^+$	32	33	50—55°	87	59	41	31

Table 2. Stereochemical results of *C*- and *O*-alkylation

Exp.	(−)R-*sec*-BuBr		(+)R-*C*-Alkylate			(+)S-*O*-Alkylate		
	$\alpha_D^{25,a)}$	Opt. Pur.$^{c)}$	$[\alpha]_D^{25,b)}$	Opt. Pur.$^{d)}$	Retention	$[\alpha]_D^{25,b)}$	Opt. Pur.$^{e)}$	Inversion
1	12.52°	29.2%	+0.97°	3.2%	11%	+4.3°	19%	66%
2	11.72°	27.3%	——	2.7%	10%	+4.9°	23%	66%
3	12.52°	29.2%	+1.4°	4.5%	15%	+5.1°	18%	62%
4	11.72°	27.3%	+4.5°	6.0%	20%	+2.4°	10%	23%

a) Neat, l=1 dm. *b*) Solvent $\mathrm{CHCl_3}$, $c=5\sim15$. *c*) Based on a calculated maximum value of α_D −42.92°.[5]
d) Calculated by the measured $[\alpha]_D$ of III and $[\alpha]_{D\,max}$ 9.9°.[4] *e*) Calculated by $[\alpha]_D$ of IV and $[\alpha]_{Dmax}$ 25.07°.[4]

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1) L. H. Sommer and W. D. Korte, *J. Org. Chem.*, **35**, 22 (1970).

2) H. Hart and H. S. Eleuterio, *J. Amer. Chem. Soc.*, **76**, 516 (1954), reported *O*-alkylation 100% inversion and *C*-alkylation 56—82% inversion of configuration.

3) M. Suama and K. Ichikawa, *Nippon Kagaku Zasshi*, **92**, 252 (1971).

4) F. Nerdel and E. Henkel, *Chem. Ber.*, **86**, 1002 (1953). (+)S-4-methyl-2-hexanone, $[\alpha]_{Dmax}^{20}$+9.9° (neat, d 0.820). R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **105**, 830 (1914). (+)S-*sec*-butyl acetate, $[\alpha]_D^{20}$ 25.43° (neat, *d* 0.873), 25.07° ($\mathrm{CHCl_3}$, *c* 5), 25.87° (EtOH, *c* 5).

5) D. G. Goodwin and H. R. Hudson, *J. Chem. Soc.*, *B*, **1968**, 1333.

6) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).