711. *Partial Asymmetric Synthesis with Keto-esters. Part III.**

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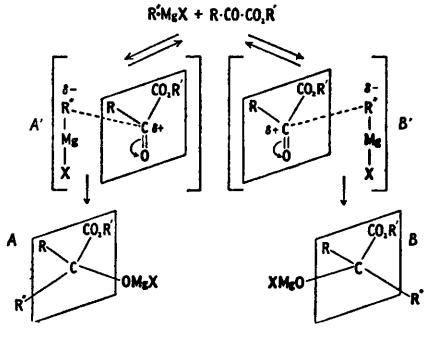
The experimental results described in Parts I and II are correlated. In partial asymmetric syntheses originating in interaction of Grignard reagents and the (−)-menthyl esters of α-, γ-, and δ-keto-acids the controlling factor is the extent of equilibration in the transition complex which is postulated as preceding the formation of the magnesium compound and is, in many cases, modified by precipitation of the product.

In Parts I and II (preceding papers) are described investigations into the extent of partial asymmetric synthesis occurring during the action of certain Grignard reagents on (−)-menthyl esters of some keto-acids.

The idea that the carbonyl group in the (−)-menthyl ester of an α-keto-acid could be stereospecifically polarised (induced asymmetry) appears to be dismissed by the results of Jamison and Turner (*J.*, 1941, 538) and of Glazer and Turner (*J.*, 1949, S 169) in their study of the mutarotation of such esters in alcoholic solution, it being shown that hemi-acetal formation sufficiently accounts for the observed phenomena :

$$\underset{(+)}{\mathrm{R{-}C(OEt)(OH){-}CO_2{\cdot}C_{10}H_{19}}} \underset{-\mathrm{EtOH}}{\overset{+\mathrm{EtOH}}{\rightleftharpoons}} \mathrm{R{\cdot}CO{\cdot}CO_2{\cdot}C_{10}H_{19}} \underset{-\mathrm{EtOH}}{\overset{+\mathrm{EtOH}}{\rightleftharpoons}} \underset{(-)}{\mathrm{R{-}C(OH)(OEt){-}CO_2{\cdot}C_{10}H_{19}}}$$

That there is a strong *chemical* influence by the ester group on the α-keto-group is shown by the fact of this hemi-acetal formation, which is peculiar to α-keto-esters; when methylene groups are interposed between the keto-group and the ester group any chemical inductive or electromeric effect between these groups is damped out.



In the case of the mutarotation of alcoholic solutions of (−)-menthyl esters of α-keto-acids, a real equilibrium can be attained between the hemi-acetals. An "asymmetric reaction" (Turner and Harris, *Quart. Reviews*, 1947, **1**, 299) occurs, but it cannot be made the precursor of an asymmetric *synthesis* since the hemi-acetals exist only in solution in presence of excess of alcohol, and removal of the (−)-menthyl group, such as would be necessary in order to provide a formal partial asymmetric synthesis, is meaningless.

In the well-established partial asymmetric syntheses (McKenzie and his co-workers, references in Parts I and II) which occur as a result of the interaction of Grignard reagents and the (−)-menthyl esters of α-keto-acids, equilibration must presumably take place to some extent at the transition complex stage (see inset), before precipitation of the magnesium complexes.

The discovery (Reid and Turner, *J.*, 1949, 3365) that the interaction of acetophenone, zinc, and (−)-menthyl bromoacetate is accompanied by partial asymmetric synthesis bears strongly on this point. In the present work the partial asymmetric synthesis observed with (−)-menthyl benzoylformate and methylmagnesium bromide leads to a product, atrolactic acid, which is largely antimeric with that produced in the partial asymmetric synthesis

* Part II, preceding paper.

involving (−)-menthyl pyruvate and phenylmagnesium bromide. On use of 1·25 molecular proportions of Grignard reagent to one of ester, the first route gave atrolactic acid with $[\alpha]^{25}_{5461}$ −9·3° and the second route an acid with $[\alpha]^{20}_{5461}$ +8·1° (rotations in absolute ethyl alcohol). By the second route, however, the yield of acid was only 50% owing to interaction of the Grignard reagent with the ester grouping (glycol formation), whereas by the first route a 97% yield of atrolactic acid was obtained. It is therefore impossible to assess the significance of the rotation figures.

In comparison with the present results it may be noted that McKenzie and Ritchie (*Biochem. Z.*, 1932, **250**, 376) investigated the partial asymmetric synthesis of 4-methoxyatrolactic acid by two routes. Interaction of (−)-menthyl *p*-methoxybenzoylformate and methylmagnesium iodide gave a final acid with $[\alpha]^{25}_{5461}$ −15·9°, whereas interaction of (−)-menthyl pyruvate and *p*-methoxyphenylmagnesium bromide led to an acid with $[\alpha]^{25}_{5461}$ +9·4°:

$$MeO{\cdot}C_6H_4{\cdot}CO{\cdot}CO_2{\cdot}\overset{(-)}{C_{10}H_{19}} \xrightarrow[\text{etc.}]{MeMgI} MeO{\cdot}C_6H_4{\cdot}CMe(OH){\cdot}CO_2H\ [\alpha]^{25}_{5461}\ -15{\cdot}9^\circ$$

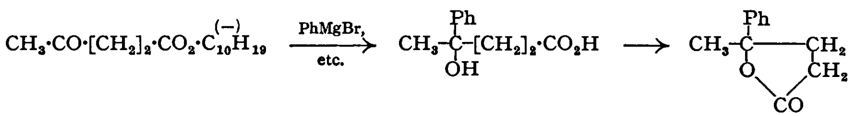
(Optically pure, $[\alpha]^{25}_{5461}$ −61·7°)

$$Me{\cdot}CO{\cdot}CO_2{\cdot}\overset{(-)}{C_{10}H_{19}} \xrightarrow[\text{etc.}]{MeO{\cdot}C_6H_4{\cdot}MgBr} MeO{\cdot}C_6H_4{\cdot}CMe(OH){\cdot}CO_2H\ [\alpha]^{25}_{5461}\ +9{\cdot}4^\circ$$

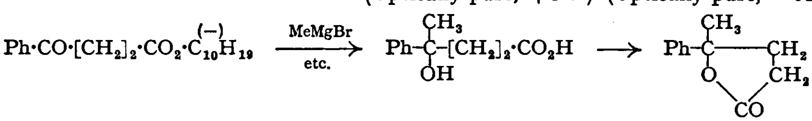
(Optically pure, $[\alpha]^{25}_{5461}$ +61·0°)

Since in these cases the degree of possible partial asymmetric synthesis depends on the difference in thermodynamic stability of the two diastereoisomeric transition complexes, a similar state of affairs should obtain when Grignard reagents react with (−)-menthyl esters of keto-acids other than those of the α-type.

Partial asymmetric synthesis has not hitherto been observed in the interaction of γ-keto-esters of active alcohols with Grignard reagents. We find that the possibility is realisable, as the following results show:



$[\alpha]^{25}_{5461}$ +0·73° (EtOH) (Optically pure, +5·7°) $[\alpha]^{25}_{5461}$ −7·7° (EtOH) (Optically pure, −61·9° ± 0·4°)



$[\alpha]^{25}_{5461}$ −0·97° (EtOH) (Optically pure, −5·7°) $[\alpha]^{25}_{5461}$ +10·2° (EtOH) (Optically pure, +61·8° ± 0·5°)

(Rotations for the acid relate to material obtained by total acidification of alkaline solutions.)

With increasing numbers of carbon atoms between the ester group and the keto-group the difference between the thermodynamic stabilities of the pairs of products of interaction with Grignard reagents must gradually decrease. We have, however, found that partial asymmetric synthesis of 5-hydroxy-5-phenylhexanoic acid occurs when (−)-menthyl γ-acetylbutyrate is treated with phenylmagnesium bromide and when (−)-menthyl γ-benzoylbutyrate is treated with methylmagnesium bromide:

$$CH_3{\cdot}CO{\cdot}[CH_2]_3{\cdot}CO_2{\cdot}\overset{(-)}{C_{10}H_{19}} \xrightarrow[\text{etc.}]{PhMgBr} CH_3{-}C(Ph)(OH){-}[CH_2]_3{\cdot}CO_2H$$

Lactone: $[\alpha]^{25}_{5461}$ −2·52° (EtOH)

$$Ph{\cdot}CO{\cdot}[CH_2]_3{\cdot}CO_2{\cdot}\overset{(-)}{C_{10}H_{19}} \xrightarrow[\text{etc.}]{MeMgBr} Ph{-}C(CH_3)(OH){-}[CH_2]_3{\cdot}CO_2H$$

Lactone: $[\alpha]^{25}_{5461}$ +2·9° (EtOH)

The extent of partial asymmetric synthesis cannot be estimated since the rotations of the optically pure lactones are unknown.

Neither the interaction of (−)-menthyl ω-acetylpelargonate and phenylmagnesium bromide nor that of (−)-menthyl ω-benzoylpelargonate and methylmagnesium bromide was accompanied by measurable partial asymmetric synthesis.

The background to the present investigation is admirably given by Ritchie (*Adv. Enzymology*, 1947, **7**, 65. See also Tiffeneau, Lévy, and Ditz, *Compt. rend.*, 1931, **192**, 955; *Bull. Soc. chim.*, 1935, **5**, 1848, 1855; Roger, *J.*, 1939, 108; Brokaw and Brode, *J. Org. Chem.*, 1948, **13**, 194).

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