94. *The Mutarotation of Ethyl-alcoholic Solutions of l-Menthyl Benzoylformate.*

By Margaret M. Jamison and E. E. Turner.

The mutarotation at the ordinary temperature of ethyl-alcoholic solutions of *l*-menthyl benzoylformate described by McKenzie and Mitchell (*Biochem. Z.*, 1929, **208**, 456) is shown to require the presence of traces of water. In absolute alcohol the mutarotation is too rapid to be measured at the ordinary temperature, but becomes measurable at 0°. Preference is expressed for the view that mutarotation depends on hemiacetal formation between the ethyl alcohol and the ester.

McKenzie (J., 1904, **85**, 1249) showed that when *l*-menthyl benzoylformate reacted with methylmagnesium iodide, unequal amounts of the diastereoisomeric menthyl atrolactates were formed : saponification of the product gave an optically active atrolactic acid. This was followed by numerous asymmetric syntheses of a similar type. In 1929, McKenzie and Mitchell (*loc. cit.*) made the interesting observation that in certain solvents (Table I) *l*-menthyl benzoylformate exhibited mutarotation and that in others (Tables II*a* and II*b*) it did not :

TABLE I.	TABLE II.	
	a.	*b.*
Ethyl alcohol	Acetone	Methyl alcohol
n-Propyl alcohol	Anisole	Allyl alcohol
n-Butyl alcohol	Benzene	*iso*Propyl alcohol
*iso*Butyl alcohol	Chloroform	*tert.*-Amyl alcohol
l-Amyl alcohol	Ether	*sec.*-Octyl alcohol

Similar observations were made with other keto-esters (McKenzie and Mitchell, *Biochem. Z.*, 1930, **224**, 241; 1931, **228**, 471; McKenzie and Ritchie, *ibid.*, 1931, **231**, 412; **237**, 1; 1932, **250**, 376; McKenzie and Christie, *ibid.*, 1935, **277**, 426 : the results were summarised by McKenzie in 1936, *Ergebn. Enzymforsch.*, **5**, 49).
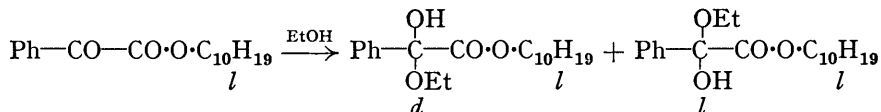
McKenzie connected the results of the earlier and the later series of investigations, and, at a time when the conception of the carbonyl group was attracting considerable attention, saw in his observations evidence for " induced asymmetry " of the carbonyl group. *l*-Menthyl benzoylformate was assumed to be capable of exhibiting diastereo-isomerism, expressed by the two forms :

$$\text{Ph—}\overset{+}{\text{C}}\text{O—CO·O·C}_{10}\text{H}_{19}^{-} \qquad\qquad \text{Ph—}\overset{-}{\text{C}}\text{O—CO·O·C}_{10}\text{H}_{19}^{-}$$

In alcohol and Table I solvents generally, mutarotation was observed and was attributed to the slow conversion of the ester into unequal amounts of the above diastereoisomerides. In ether and Table II solvents generally, mutarotation was not observed, and the conversion was therefore assumed to be too fast to be measured.   Thus, when an ethereal solution of *l*-menthyl benzoylformate was treated with a Grignard reagent, the latter met unequal amounts of the two diastereoisomerides and so asymmetric synthesis became possible.

We are not aware that any explanation other than this has been offered for the results of the Grignard synthesis, but hemiacetal formation has been considered (McKenzie and Mitchell, *loc. cit.*; Ebert and Kortüm, *Ber.*, 1931, **64**, 342) as an explanation of the mutarotation of ethyl-alcoholic solutions of *l*-menthyl benzoylformate.   This, in absence of the Grignard results, would explain why mutarotation cannot be observed in ether, benzene, etc., and the fact that it was not observed with certain alcohols other than ethyl could not be regarded as evidence against the hemiacetal theory.   It must be pointed out, in favour of the hemiacetal view, that since such compounds as mesoxalic esters form isolable hemiacetals when treated with ethyl alcohol (cf. Curtiss and Spencer, *J. Amer. Chem. Soc.*, 1909, **31**, 1055), it is at least unlikely that menthyl benzoylformate, with two electron-attracting groups attached to the carbonyl group, would not tend to form a hemiacetal when dissolved in excess of ethyl alcohol.

Theoretically, it should be possible to distinguish by kinetic measurements between " asymmetric induction " at the carbonyl group and hemiacetal formation.   The former process would clearly be a unimolecular one in all circumstances, while the addition :

$$\underset{l}{\text{Ph—CO—CO·O·C}_{10}\text{H}_{19}} \xrightarrow{\text{EtOH}} \underset{d}{\text{Ph—}\overset{\overset{\text{OH}}{|}}{\underset{\underset{\text{OEt}}{|}}{\text{C}}}\text{—CO·O·C}_{10}\text{H}_{19}} + \underset{l}{\text{Ph—}\overset{\overset{\text{OEt}}{|}}{\underset{\underset{\text{OH}}{|}}{\text{C}}}\text{—CO·O·C}_{10}\text{H}_{19}}\ l$$

should show first-order kinetics when the alcohol is present in excess, but second-order kinetics when alcohol and ester are present in approximately equivalent amounts.   We have endeavoured to examine this experimentally.   The conditions favourable to the bimolecular reaction could not be realised, because the ester is sparingly soluble in ethyl alcohol, and when the ester and alcohol are mixed in equivalent quantities in inert solvents mutarotation is either too slow or too slight to be detectable.   Were the mutarotations observed by McKenzie and his co-workers due to the asymmetric induction effect, it is surprising that it did not occur in so many solvents : absence of mutarotation when alcohol and the ester were mixed in an inert solvent fits in with the hemiacetal explanation, since hemiacetal formation may well require a considerable excess of alcohol to make it appreciable.

McKenzie and Mitchell (*loc. cit.*) found that in ethyl alcohol dried over quicklime and then over calcium the specific rotation of *l*-menthyl benzoylformate changed during 24 hours from $[\alpha]_{5461}^{25°} - 54°$ to $- 59°$ and thereafter remained constant ($c = 2 \cdot 9988$; α changed from $- 3 \cdot 21°$ to $- 3 \cdot 56°$; $l = 2$).   They concluded (*Biochem. Z.*, 1930, **224**, 241) that the presence of small quantities of water did not affect the mutarotations they observed with their alcoholic solutions.

In attempting to repeat their experiments, we have found that at $18 \cdot 8°$ solutions of the

ester in ethyl alcohol containing amounts of water of the order of 0·05—0·10% exhibit the type of mutarotation they describe, the final specific rotation $[\alpha]_{5461}^{18\cdot8°}$ being $-60\cdot8°$ ($l = 2$; $c = 4\cdot783$).   With *absolute* ethyl alcohol we observed no mutarotation at 18·8°, the solution showing from the very outset the specific rotation $-60\cdot8°$.   This result suggested that in anhydrous alcohol mutarotation is too rapid to be measurable at the ordinary temperature, but opened up the possibility that it might be observable at lower temperatures.   In fact, we were able to demonstrate it at 0°.   Moreover, addition of small quantities of water to an absolute-alcoholic solution prepared at 18·8° had no observable effect on the specific rotation either immediately or after 24 hours, thus indicating that mutarotation had already proceeded to completion.   The identity of the final rotations in alcohols of different water content suggests that the equilibrium composition is independent of the water concentration if the latter is low : it is unlikely that the figure, $-60\cdot8°$, is the result of change in equilibrium composition being exactly compensated by the change in solvent property.

The decelerating effect of water on the observed mutarotation approaches a constant value which is attained when about 0·15% of water is present.   We have demonstrated this by quantitative study of the mutarotation of *l*-menthyl benzoylformate in alcohol containing varying amounts of water.   The mutarotations all followed the first-order law, and are summarised below, k being calculated in decadic logarithms here and throughout.

EtOH, %.	Time of first reading after dissolving (mins.).	$[\alpha]_{5461}^{18\cdot8°}$.		$k \times 10^3$ (min.$^{-1}$) at 18·8°.
		Initial.	Final.	
99·98	10	$-54\cdot45°$	$-60\cdot8°$	13·0
99·96	11	$-51\cdot8$	$-60\cdot8$	0·93
99·86	13	$-51\cdot3$	$-60\cdot5$	0·73
99·05	3	$-51\cdot6$	$-60\cdot8$	0·78

In all experiments, $l = 2$.   In the first three experiments, $c = 4\cdot783$, and in the last, $c = 3\cdot5175$.

With different samples of ethyl alcohol, freed as far as possible from all traces of water, three experiments gave the following results :

c.	Time of first reading (mins.).	$[\alpha]_{5461}^{0°}$.		$[\alpha]_{5461}^{18\cdot8°}$.	$k \times 10^3$ (min.$^{-1}$) at 0°.
		Initial.	Final.	Final.	
1·775	2·25	$-58\cdot0°$	$-64\cdot0°$	—	—
2·371	3·6	$-50\cdot5$	$-64\cdot7$	$-60\cdot8°$	41
2·050	2·6	$-52\cdot9$	$-63\cdot9$	—	170

The divergence between the values of k obtained on two different occasions is an indication of the sensitivity of the change to traces of water.   It may be noted that the initial specific rotation of *l*-menthyl benzoylformate in " absolute " alcohol could be used to diagnose the freedom of the solvent from water, as consideration of the above figures shows.

Our first explanation of the mutarotational effects observed was based on the following scheme :

In absence of any evidence to the contrary, it may be assumed that the final product in anhydrous alcohol or in alcohol containing small amounts of water is (IV), since the final specific rotation is $-60\cdot8°$ in all cases.

A simple explanation of the changes observed then appeared to be that (I) $\longrightarrow$ (II)

and (II) ——→ (III) were fast reactions, but (III) ——→ (IV) and (III) ——→ (II) slow reactions. If, then, (II) ——→ (IV) is much slower than (III) ——→ (IV), the deceleration due to water is accounted for. On the other hand, we know that in absence of water (I) ——→ (IV) is a very rapid process. Moreover, it seems extremely unlikely that water, which shows no tendency to combine with (I) in absence of alcohol, should combine with it when alcohol is present in large excess. In this connexion it must be remembered that the relatively very stable chloral hydrate, analogous to (III), can be converted by the action of alcohol in excess into chloral alcoholate, analogous to (IV). Similarly, chloral alcoholate, dissolved in excess of *iso*amyl alcohol, gives chloral "*iso*amyl alcoholate" (Gadamer, *Arch. Pharm.*, 1905, **243**, 30).

In previous communications (Jamison and Turner, J., 1938, 1646; 1940, 264) emphasis has been laid on the large quantitative difference, almost amounting to a qualitative one, between the condition of acid–base combinations in hydroxylic solvents on the one hand and non-hydroxylic solvents on the other. Particular attention may also be directed to the extraordinary effect on the activation of the cinchonidine salt of *N*-benzenesulphonyl-8-nitro-1-naphthylglycine of traces of alcohol in the main solvent used (chloroform).

There is little evidence, apart from the results now communicated, as to the effect upon the velocity of a reaction occurring in ordinary "absolute alcohol" of removing the last traces of water, the reason possibly being that hitherto it was not to be expected that such an inquiry would be fruitful.

Taking the situation as it is, however, it does not seem impossible that, compared with ordinary "absolute alcohol," anhydrous alcohol may behave as possessing only weak proton-donating properties. The point is at any rate worth examining, and leads to the suggestion that, although in slightly wet alcohol reactions of an ionic type begin the process measured as a mutarotation, yet in anhydrous alcohol "hydrogen bond" or resonance complexes such as (V) are concerned. The intra-molecular rearrangement of (V) to (IV) should be extremely rapid compared with the bimolecular processes involved in the formation of (II).

$$C_{10}H_{19}\cdot O\cdot CO \overset{Ph}{\underset{}{>}}C{=}O \ldots HOEt \quad (V.)$$

We conclude, therefore, that in anhydrous alcohol the mechanism of the rapid mutarotation observed at 0° is that just outlined, and that in alcohol containing small amounts of water an ionic mechanism functions, but that (III) is not necessarily an important intermediate in the conversion of (I) into (IV).

The mechanism of the asymmetric syntheses by the Grignard method may be compared with the above mechanism for the anhydrous alcohol solution :

$$\text{(A)} \quad >\!C{=}O \longrightarrow >\!C{=}O{\to}Mg\}X \overset{R}{\longrightarrow} >\!CR{-}OMg\}X$$

$$\text{(B)} \quad >\!C{=}O + RMgX \longrightarrow >\!CR{-}OMg\}X$$
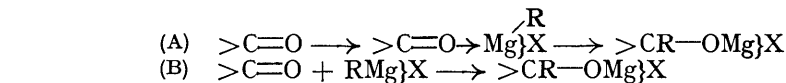
Addition of RMgX is different from the addition of EtOH because it is irreversible. For this reason, it seems probable that mechanism (A) more truly represents the facts than (B). The first sequence of changes would clearly permit, indeed require, an asymmetric synthesis, because of the different stabilities of the two intermediate complexes.

It must, in conclusion, be pointed out, that, although in the Grignard reactions, asymmetric synthesis is an established fact, there is so far no evidence that the mutarotation observed with an alcoholic solution of *l*-menthyl benzoylformate is due to anything more complex than simple solvation : the point remains unproven.

EXPERIMENTAL.

l-Menthyl benzoylformate, prepared as described by McKenzie (J., 1904, **85**, 1249), was crystallised from ethyl alcohol and dried in a vacuum over sulphuric acid : it was then free from possible traces of solvent of crystallisation (Found : C, 75·0; H, 8·4. Calc. : C, 75·0; H, 8·4%).

The absolute ethyl alcohol used was obtained by leaving the commercial material over quicklime for several weeks, heating it under reflux with barium oxide, and finally distilling it from fresh barium oxide through a Widmer column. Precautions were taken to exclude moisture, and the alcohol was used within a few minutes of being distilled. Alcohols of definite water

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content were made by adding water to the absolute alcohol, the percentages mentioned being those by weight.

Mutarotations at $18.8°$.—In these experiments the l-menthyl benzoylformate was weighed in a 20-c.c. stoppered flask (if necessary then dried in a vacuum over sulphuric acid), and the alcohol added, with temperature control.

(1) 99.98% Alcohol; $c = 4.783$. The first polarimetric reading ($l = 2$) was made 10 mins. after wetting ester with solvent; $\alpha_{5461}^{18.8°}$ changed from $-5.21°$ to $-5.82°$, whence change in $[\alpha]_{5461}^{18.8°}$ was from $-54.45°$ to $-60.8°$; $k = 0.013$ (min.$^{-1}$) (limits, 0.0155 and 0.0123).

(2) 99.96% Alcohol; $c = 4.783$. First reading in 11 mins. Change in $\alpha_{5461}^{18.8°}$, $-4.96°$ to $-5.82°$. Change in $[\alpha]_{5461}^{18.8°}$, $-51.8°$ to $-60.8°$; $k = 0.00093$ (min.$^{-1}$) (limits, 0.0010 and 0.00087).

(3) 99.86% Alcohol; $c = 4.783$. First reading at 0.22 hr. Change in $[\alpha]_{5461}^{18.8°}$, $-51.3°$ to $-60.5°$. Time (t, in hrs.) is reckoned from 0.22 hr.

t	0.0	2.0	3.0	5.0	6.0	7.0	8.0	9.0	12.0	∞
α_t	$-4.91°$	$-5.08°$	$-5.15°$	$-5.26°$	$-5.315°$	$-5.355°$	$-5.385°$	$-5.42°$	$-5.51°$	$-5.79°$
k (hr.$^{-1}$)	—	0.0465	0.046	0.044	0.0445	0.0435	0.042	0.041	0.041	—

$$k = 0.044 \text{ (hr.}^{-1}) \text{ or } 0.00073 \text{ (min.}^{-1}).$$

(4) 99.05% Alcohol; $c = 3.5175$. First reading in 3 mins.; $\alpha_{5461}^{18.8°}$ changed from $-3.63°$ to $-5.82°$, $[\alpha]_{5461}^{18.8°}$ from $-51.6°$ to $-60.8°$; $k = 0.00078$ (min.$^{-1}$) (limits, 0.00070 and 0.00088).

Readings in 100% *alcohol at* $18.8°$. (1) $c = 4.783$, $\alpha_{5461}^{18.8°}$ $-5.82°$, $[\alpha]_{5461}^{18.8°}$ $-60.8°$; first reading in 24 mins.; no change in 24 hours. (2) $c = 4.783$, $\alpha_{5461}^{18.8°}$ $-5.81°$, $[\alpha]_{5461}^{18.8°}$ $-60.7°$; no change on keeping.

Mutarotations in 100% *alcohol at* $0°$. (1) $c = 2.3710$; first reading 3.6 mins. after mixing; t reckoned from this stage.

t	0.0	0.6	1.6	2.1	2.45	3.75	6.5	6.8	7.6
α	$-2.52°$	$-2.56°$	$-2.61°$	$-2.63°$	$-2.66°$	$-2.73°$	$-2.86°$	$-2.86°$	$-2.89°$
k (min.$^{-1}$)	—	0.0420	0.0368	0.0348	0.0389	0.0406	0.0436	0.0416	0.0421

t	9.25	10.8	11.15	11.6	11.9	15.2	16.0	∞	
α_t	$-2.88°$	$-2.98°$	$-2.99°$	$-2.99°$	$-3.03°$	$-3.09°$	$-3.11°$	$-3.23°$	
k (min.$^{-1}$)	0.0332	0.0420	0.0423	0.0406	0.0462	0.0464	0.0483	—	

$$k = 0.041 \text{ (min.}^{-1}).$$

(2) $c = 2.0500$; $k = 0.17$ (min.$^{-1}$) (limits, 0.19 and 0.14).

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