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The Action of the Grignard Reagent on Camphoric and Isocamphoric Esters.

By

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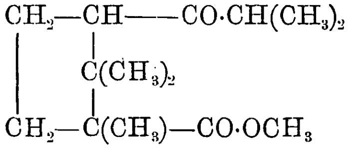
In a recently published paper on the action of the GRIGNARD reagent on *o*-phthalic esters (This Journ., 1909, Vol. **27**, Art. 4), it was shown that the two CO_2R groups in these esters, contrary to those in succinic and terephthalic esters, exert steric hindrance in carrying out the GRIGNARD's reaction, producing derivatives of phthalide, or, as is more often the case, those of phthalane. In the case of succinic and terephthalic esters, the normal product of the reaction is a glycol, and it was pointed out that this difference in the action of the GRIGNARD reagent on the esters of *o*-phthalic acid on the one hand and on those of succinic and terephthalic acids on the other was most probably due to the fact that the two CO_2R groups in *o*-phthalic esters are in the *cis*-position, while those in succinic and terephthalic esters are in the *trans*-position. It was further pointed out that, from the point of view thus attained by the study of the action of the GRIGNARD reagent on *o*-phthalic esters, GRAEBE's space formula for benzene is to be preferred to all others.

In order to obtain, if possible, further confirmation of the view thus expressed, the behaviour of camphoric and isocamphoric esters toward the GRIGNARD reagent has now been studied, these being known clearly as the *cis-trans*-isomers. If the assumption is true that the two CO_2R groups in the *cis*-position exert steric hindrance, while those in the *trans*-position do not, then by the action of the Grignard reagent, camphoric esters should produce campholides, analogous to the phthalides, while isocamphoric esters should produce glycols or some other non-condensed hydroxyl-derivatives.

In fact, this anticipation has been fully confirmed, except in the case of the action of magnesium isopropyl iodide on dimethyl camphorate. In this case, a substance has been obtained, which is considered to be a δ-ketonic ester having the constitution:



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It is known that iso-alkyl groups generally exert a more remarkable steric influence than the normal ones (compare M. Davis, Journ. Chem. Soc., 1909, **95**, 1397), and it is highly probable that here also the first isopropyl group which has entered into reaction with dimethyl camphorate has hindered the addition of a second molecule of the Grignard reagent, thus producing a ketonic ester, or, in other words, stopping the reaction at its first stage.

The Action of Magnesium Phenyl Bromide on Dimethyl d-Camphorate.

d-Camphoric acid, which was prepared by the oxidation of

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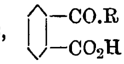
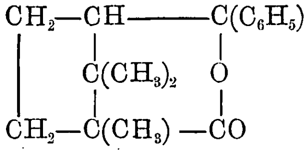
* The compounds of analogous constitution, *o*-acyl-benzoic acids, , have been recently synthesised by the action of the Grignard reagent on phthalic acid by H. Simonis and K. Arand (Ber., 1909, **42**, 3721), also compare A. Guyot and J. Catel (Bull. Soc. Chim., 1906, [iii], **35**, 551).

Japanese camphor according to the processes given by F. Wreden (Annalen, 1872, **163**, 323) and W. A. Noyes (Amer. Chem. Journ., 1894, **16**, 307), was converted into the neutral methyl ester by means of dimethyl sulphate, according to the patent method of J. D. Riedel (D.R.P., 189840 [1906] and 196152 [1908]).

Dimethyl *d*-camphorate thus prepared boils at 147–150° under 10 mm. pressure, or at 162–164° under 29 mm. pressure, while Riedel gives its boiling point as 145–147° under 20 mm. pressure. The sample was, therefore, analysed and proved to be free from impurities.

0·2213 gave 0·5101 CO_2 and 0·1739 H_2O. C=62·87; H=8·78.
$C_{12}H_{20}O_4$ requires C=63·10; H=8·85 per cent.

The reaction between dimethyl camphorate and magnesium phenyl bromide was carried out in precisely the same manner as in the case of diethyl phthalate (loc. cit.). An etherial solution of the ester was added to magnesium phenyl bromide in the proportion of 1 to 4 molecules, and the product, obtained by decomposing the resulting solution with ice and dilute sulphuric acid, was subjected to steam distillation to remove the excess of bromobenzene and diphenyl, formed as a by-product. The residual oil soon solidified, and the solidified mass was finely pulverised and dried in a vacuum over sulphuric acid. In order to remove the oil still adhering, the yellowish powder thus obtained was rubbed in a mortar with a small quantity of alcohol which was then well sucked, and the product recrystallised from hot alcohol. Small colourless needle-shaped crystals with a melting point of 154–155° were thus obtained. They are easily soluble in ether, benzene, carbon bisulphide, acetone, chloroform, and hot alcohol, and difficultly soluble in cold alcohol, and petroleum ether. On analysis the results obtained agreed with those required by diphenylcampholide,



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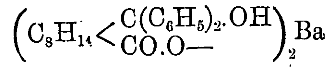
0·1541 gave 0·4664 CO_2 and 0·1043 H_2O. $C=82·54$; $H=7·75$.
$C_{22}H_{24}O_2$ requires $C=82·45$; $H=7·56$ per cent.

That this substance is diphenylcampholide was proved by the action of alcoholic potash and of nitric acid upon it.

The action of alcoholic potash :—Diphenylcampholide, dissolved in alcohol, was heated on a water-bath for about twenty hours with an excess of alcoholic potash. On adding a large amount of water, a small quantity of the original substance separated out, and was filtered off. The filtrate was evaporated on a water-bath with repeated additions of water to remove the alcohol, and the aqueous solution was acidified with hydrochloric acid. White amorphous precipitates, thus formed, were collected on a filter, well washed, and dried in a vacuum desiccator over sulphuric acid. The acidic substance thus obtained contains water of crystallisation, and melts indefinitely above 100°, with previous sintering at about 60°. When this substance is dissolved in ether, the water of crystallisation separates out, and on driving off the ether from the etherial solution, an oily substance is left. As thus this substance could not be purified, its barium salt was prepared by adding barium chloride to a solution of its sodium salt. After drying it at 120°, it was analysed and proved to be barium diphenyloxycampholate,



$\left(C_8H_{14}<\begin{matrix}C(C_6H_5)_2.OH\\CO.O—\end{matrix}\right)_2Ba$:—

0·2458 dried salt gave 0·0699 $BaSO_4$. $Ba=16·73$.
$C_{44}H_{50}O_6Ba$ requires $Ba=16·92$ per cent.

Diphenyloxycampholic acid obtained by the hydrolysis of diphenylcampholide, being a γ-oxy-acid, should easily yield a lactone, as was in fact found to be the case. A small quantity of the acid was weighed in a platinum boat, and kept in an air-bath at 100° until the constant weight was attained. It was then analysed:—

0·2339 gave 0·7009 CO_2 and 0·1587 H_2O. C=81·73; H=7·41.
$C_{22}H_{24}O_2$ requires C=82·45; H=7·56 per cent.

Thus by merely heating to 100°, the lactone was formed. The same result was also obtained by heating the acid with an excess of acetic anhydride on a water-bath for about five hours.

The action of fuming nitric acid:—Diphenylcampholide dissolves easily in fuming nitric acid with a considerable evolution of heat. On the addition of water to the solution, brownish precipitates separated out. A chloroform solution of the precipitates was boiled with animal charcoal, filtered, and the filtrate was evaporated on a water-bath. Small yellowish crystals melting at 224–225°, easily soluble in chloroform, and insoluble in alcohol, ether, and petroleum ether, were thus obtained, which gave the following results on analysis:—

0·1275 gave 0·2997 CO_2 and 0·0531 H_2O. C=64·11; H=4·66.
0·1873 gave 11·12 c.c. N_2 at 760 mm. and 18°C. N=6·82.
$C_{22}H_{22}O_6N_2$ requires C=64·36; H=5·41; N=6·83 per cent.

Thus the substance is dinitrodiphenylcampholide.

Diphenylcampholide is very stable toward the action of oxidising agents. Thus even when it was heated with chromic acid mixture to 150–155° for about twenty hours, only a very small portion of the substance was attacked, and, on repeated recrystallisation from alcohol, a small quantity of a substance melting at

200° was isolated. But the quantity of it was so small that further investigation was impossible.

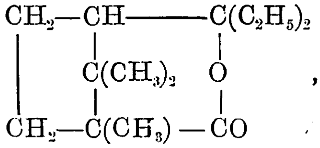
The Action of Magnesium Ethyl Iodide on Dimethyl d-Camphorate.

As the reaction product, an yellowish oil was obtained, the main part of which distilled (I) at 170–172° under 6–7 mm. pressure, or (II) at 176–178° under 16 mm. pressure. It was analysed with the following results:—

(I) 0·2749 gave 0·7489 CO_2 and 0·2619 H_2O. $C=74{\cdot}30$; $H=10{\cdot}65$.

(II) 0·2362 gave 0·6437 CO_2 and 0·2257 H_2O. $C=74{\cdot}32$; $H=10{\cdot}68$.

$C_{14}H_{24}O_2$ requires $C=74{\cdot}93$; $H=10{\cdot}79$ per cent.

Diethylcampholide,  , crystallises into small plates, melting at 37–38°, soluble in alcohol, ether, petroleum ether, chloroform, benzene, acetone, and carbon bisulphide.

The action of alcoholic potash on diethylcampholide:—The substance, dissolved in alcohol, was heated with an excess of alcoholic potash on a water-bath for about twenty hours. When the solution was treated in the same manner as in the preceding case, a brownish oil separated out on acidification with hydrochloric acid. On being allowed to stand for a long time, a small portion of the oil solidified, and the solid was collected and left on a porous tile to remove the oil still adhering. It was then dissolved in alcohol, and water was added to the solution drop by drop until turbidity began to appear. On standing, long needle-shaped crystals separated out, which melted between 90–98°. They were dissolved in alkali and reprecipitated with hydrochloric acid, but no improvment in the melting point was observed. As the substance was scanty, no further study of it was attempted.

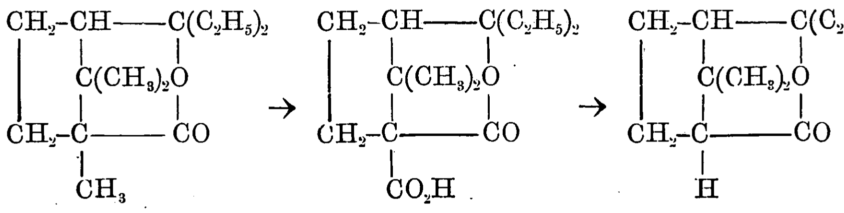
The oxidation of diethylcampholide :—Diethylcampholide was heated with chromic acid mixture on a water-bath for five hours. The oxidation went on with a brisk evolution of gases, and on cooling, the oily substance solidified into fine needles. They were then repeatedly recrystallised from dilute alcohol, and beautiful lustrous feathery crystals, with a melting point of 60°, were obtained. The substance is very easily soluble in alcohol, ether, benzene, chloroform, carbon bisulphide, acetone, and petroleum ether. It gave the following results on analysis:—

0·1039 gave 0·2834 CO_2 and 0·0994 H_2O. $C=73·68$; $H=10·60$.
$C_{13}H_{22}O_2$ requires $C=74·21$; $H=10·56$ per cent.

The molecular weight of the substance was determined by the cryoscopic method, and a value well coinciding with the above formula was obtained:—

0·2532 in 17·56 benzene caused 0·335° depression. $M=215·2$.
$C_{13}H_{22}O_2$ requires $M=210·2$.

On comparing this formula, $C_{13}H_{22}O_2$, with that of the original substance, $C_{14}H_{24}O_2$, it may be seen that no increase in oxygen but a diminution of CH_2 took place by the oxidation. This means that one of the three methyl groups in the camphor molecule had been replaced by a hydrogen atom, and the following scheme of the oxidation process seems to be most probale:—



The substance is, therefore probably, diethylapocampholide. That this substance is a lactone may easily be proved by the action of alkali on it.

The action of alcoholic potash on diethylapocampholide :—By the actión of alcoholic potash on diethylapocampholide, after the usual treatment, white precipitates were obtained on acidification. The precipitates, on standing over night, crystallised in feathery needles, melting at 60°, with the following composition:—

0·0797 gave 0·2173 CO_2 and 0·0770 H_2O. C=74·36 ; H=10·80.
$C_{13}H_{22}O_2$ requeris C=74·21 ; H=10·56 per cent.

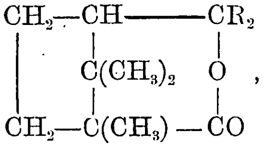
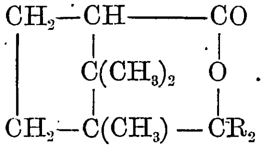
The substance is, no doubt, nothing but the original substance, and the oxy-acid, first produced by the action of alcoholic potash, must have been brought back again into its lactone by the action of an excess of hydrochloric acid.

The Action of Magnesium Methyl Iodide on Dimethyl d-Camphorate.

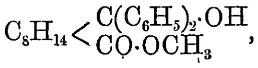
By the action of magnesium methyl iodide on dimethyl camphorate, carried out in the usual manner, an oily substance was obtained, almost all of which distilled with steam. The oil was extracted with ether from the distillate, and was fractionated under a reduced pressure of 10 mm., after driving off the ether. The main part distilled at 145–147·5° as a colourless oil with a faint odour like turpentine oil. On analysis it gave the following results, agreeing well with the composition of dimethylcampholide:—

0·3520 gave 0·9434 CO_2 and 0·3226 H_2O. C=73·10 ; H=10·25.
$C_{12}H_{20}O_2$ requires C=73·39 ; H=10·30 per cent.

G. Komppa (Ber., 1908, **41**, 1039) obtained dimethylcampholide in crystalline from with a melting point of 83·5–85° by the action of magnesium methyl iodide on camphoric anhydride. In campholides, the existence of the following two isomers are possible:

(I)  , and (II)  .

And, in fact, J. Houben (Ber., 1908, **41**, 1580) obtained both of the two isomers of dibenzylcampholide by the action of magnesium benzyl chloride on camphoric anhydride. In the case of dimethylcampholide, Komppa's crystalline form and my oily one will probably be found to correspond to these two forms. Kommpa gave formula I to his dimethylcampholide without any remark on this point. I am, however, inclined to believe that my oily substance has formula I, and Kamppa's crystalline one has formula II.

As will be described hereafter, the action of magnesium phenyl bromide on dimethyl isocamphorate results in the formation of methyl diphenyl-oxy-isocampholate,  $C_8H_{14}<\begin{matrix}C(C_6H_5)_2\cdot OH\\CO\cdot OCH_3\end{matrix}$, one of the two ester groups remaining untouched. In this case, from the point of view of the steric influence, it is most natural to regard the untouched ester group as one in union with that carbon atom which carries a methyl group with it. In the case of the formation of dialkyl(aryl)campholides, the same theory must also hold true, although the intermediate product, methyl dialkyl(aryl)-oxy-campholate could not be isolated, or in other words, the campholides obtained by the action of Grignard reagents on camphoric esters must have formula I. Again, it is also most probable that in the formation of two isomeric campholides from camphoric anhydride, the one with formula I will be obtained in better yield than the other. In fact KOMPPA states in his paper that he obtained an oily substance along with the crystalline dimethylcampholide, the former being in far larger quantity than the latter. He did not, however, further examine the oily substance which should have contained the oily modification of the campholide.

The action of alcoholic potash on dimethylcampholide :—An alcoholic solution of dimethylcampholide was treated with an excess of alcoholic potash in the usual manner, and on acidifying the clear alkaline solution, white turbidity soon appeared. On letting it stand over night, an oily substance was obtained at the bottom of the vessel. The oil was extracted with ether, the etherial solution dried over calcium chloride, and the ether driven off. The residue was fractionated, when the main part of it passed over at 165–166° under 16 mm. pressure. On analysis the following results were obtained:—

0·2055 gave 0·5451 CO_2 and 0·1887 H_2O. $C=72{\cdot}36$; $H=10{\cdot}27$.
$C_{12}H_{20}O_2$ requeris $C=73{\cdot}39$; $H=10{\cdot}30$ per cent.

The oil, thus separated by acidifying the alkaline solution, is no more soluble in alkali. This fact and the results of the analysis show that the oil is the original dimethylcampholide, dimethyloxycampholic acid, formed by the hydrolysis of the campholide, having been brought back into its lactone by the action of the hydrochloric acid.

The Action of Magnesium Isopropyl Iodide on Dimethyl d-Camphorate.

The reaction product is a colourless viscous oil with a feeble odour somewhat resembling that of camphor. On fractionation, it distilled at 140–142° under 7 mm. pressure, or at 159–160° under 20–21 mm. pressure. On analysis the following results were obtained:—

0·3177 gave 0·8220 CO_2 and 0·2716 H_2O. C=70·56; H=9·56.

0·3126 gave 0·8069 CO_2 and 0·2653 H_2O. C=70·35; H=9·48.

$C_{14}H_{24}O_3$ requires C=70·00; H=10·00 per cent.

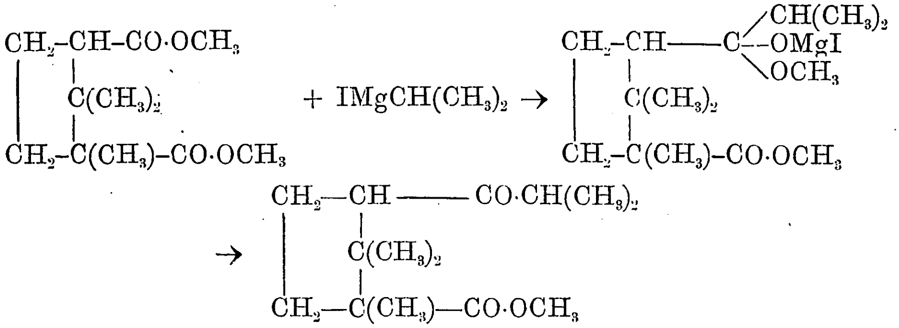
The oxidation of the substance $C_{14}H_{24}O_3$:—The oil was dissolved in benzene and shaken with an acidic solution of potassium permanganate (5%). On driving off the benzene, an oily substance was obtained, which was fractionated. The portion distilling about 150° under 7 mm. pressure gave a considerable quantity of crystals on cooling. These were recrystallised from alcohol, and the colourless needles thus obtained melted at 224–225°, and gave the following results on analysis, showing that the substance is camphoric anhydride:—

0·1002 gave 0·2424 CO_2 and 0·0701 H_2O. C=65·98; H=7·82.

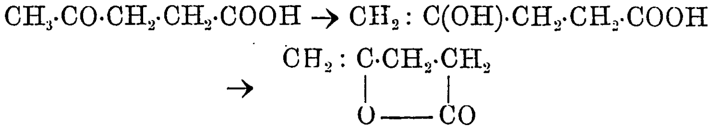
$C_{10}H_{14}O_3$ requires C=65·90; H=7·74 per cent.

The action of alcoholic potash on the substance $C_{14}H_{24}O_3$:—The oil was boiled with an excess of alcoholic potash for twenty hours, and after the usual treatment, an oil separated out on acidification. This was extracted with ether, the etherial solution dried over calcium chloride, the ether driven off, and the residue fractionated under a reduced pressure. Camphoric anhydride was again obtained in a considerable quantity.

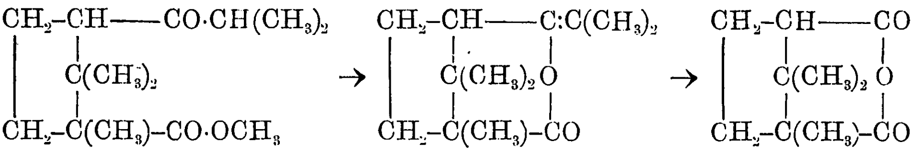
These changes can easily be explained if a constitution of methyl 1:2:2-trimethyl-3-isobutyryl-*cyclo*-pentane-1-carboxylate be given to the substance $C_{14}H_{24}O_3$ as stated in the introductory part, its formation from dimethyl camphorate and magnesium isopropyl iodide being represented as follows:—



As is known, a γ-ketonic acid, like acetylpropionic acid, is easily converted into an unsaturated lactone by long heating, according to the following scheme:—



In the formation of camphoric anhydride from the above substance $C_{14}H_{24}O_3$ by the action of potassium permangante and of alcoholic potash, dimethylmethylenecampholide might first be formed, the above δ-ketonic ester having gone through a change similar to this change of γ-ketonic acids, whence camphoric anhydride is formed by the splitting of the dimethylmethylene residue:—



The Action of Magnesium Phenyl Bromide on Dimehtyl l-Isocamphorate.

l-Isocamphoric acid was prepared from *d*-camphoric acid by the method of O. Aschan (Ber., 1889, **27**, 2005). The neutral methyl ester of this acid, hitherto unknown, was prepared by a method similar to the patent method of J. D. Riedel (loc. cit.) for the preparation of camphoric esters. The dimethyl ester is a colourless viscous oil, boiling at 165–170° under 37–38 mm. pressure, and having the following composition:—

0·2245 gave 0·5175 CO_2 and 0·1760 H_2O. $C=62{\cdot}87$; $H=8{\cdot}80$.
$C_{12}H_{20}O_4$ requires $C=63{\cdot}10$; $H=8{\cdot}85$ per cent.

The reaction between this ester and magnesium phenyl bromide was carried out quite in the same way as in the case of dimethyl camphorate, and a crystalline substance was obtained. On recrystallising it from alcohol, colourless needles melting at 105–106° were obtained, with the composition of methyl diphenyl-oxy-isocampholate:—

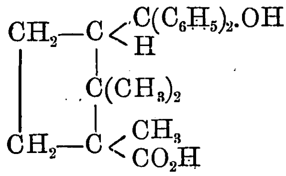
0·1831 gave 0·5261 CO_2 and 0·1365 H_2O. $C=78{\cdot}36$; $H=8{\cdot}33$.
$C_{23}H_{28}O_3$ requires $C=78{\cdot}36$; $H=8{\cdot}01$ per cent.

The substance is easily soluble in benzene, ether, carbon bisulphide, chloroform, and acetone, moderately soluble in alcohol, and glacial acetic acid, and insoluble in petroleum ether.

The saponification of the ester :—The alcoholic solution of the ester was boiled with an excess of alcoholic potash on a water-bath. On diluting the mixture with a large amount of water, a considerable quantity of the original ester separated out. The filtrate was evaporated on a water-bath to remove the alcohol, and the alkaline solution was acidified with hydrochloric acid. The white precipitates thus obtained were recrystallised from dilute alcohol. The acid thus purified is in the form of lustrous scaly crystals, melting at 214°, with the following composition:—

0·1323 gave 0·3797 CO_2 and 0·0944 H_2O. $C=78{\cdot}27$; $H=7{\cdot}98$.
$C_{22}H_{26}O_3$ requires $C=78{\cdot}02$; $H=7{\cdot}74$ per cent.

Thus the substance is diphenyl-oxy-isocampholic acid,



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a *trans*-acid, not forming its lactone easily, as is the case with *cis*-acids.

The preparation of dimethyl isocamphorate being tolerably laborious, further examination of the action of other Grignard reagents with this ester was not attempted.

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