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Conjugate Additions of Grignard Reagents to alpha, beta-Unsaturated Esters

IX. 1,4- and 1,6-Additions of *n*-Butylmagnesium Bromide to the *sec*-Butyl Ester of Sorbic Acid

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The uncatalyzed addition of *n*-butylmagnesium bromide to *sec*-butyl sorbate results in both conjugate addition and 1,2-addition. The conjugate addition is predominantly a 1,4-addition, although 1,6-addition takes place to a considerable degree. When the addition is carried out in the presence of cuprous chloride no 1,2-addition product can be isolated, and the conjugate addition takes place in good yield and almost exclusively as 1,6-addition. A mechanism which accounts for these results is suggested.

The identification and estimation of compounds has been accomplished by means of gas-liquid chromatography, infra-red spectroscopy and conventional chemical investigations.

The addition of a Grignard reagent, *e.g.* *n*-butylmagnesium bromide, to a sorbic ester may in principle lead to the formation of the following compounds, either by 1,2-additions (to the carbonyl group), by 1,4-addition (to the α,β-double bond) or by 1,6-additions (to the 2,4-diene system or to the γ,δ-double bond):

$$CH_3CH=CH-CH=CH-COOR' \xrightarrow{C_4H_9MgBr}$$

1,2-additions

$CH_3CH=CH-CH=CH-CO-C_4H_9$ I

$CH_3CH=CH-CH=CH-C(OH)(C_4H_9)_2$ II

1,4-addition

$CH_3CH=CH-\underset{\displaystyle C_4H_9}{\underset{|}{CH}}-CH_2COOR'$ III

1,6-additions

$$CH_3CH(C_4H_9)-CH=CH-CH_2COOR' \quad IV$$

$$CH_3CH(C_4H_9)-CH_2CH=CH-COOR' \quad V$$

Furthermore, products resulting from the occurrence of combinations of these addition types could be formed, such as:

$$CH_3CH=CH-CH(C_4H_9)-CH_2CO-C_4H_9 \quad VI$$

In the literature additions of Grignard reagents to the double bonds of 2,4-alkadienoic esters are apparently only reported by Kohler and his school. Kohler and Butler [1] added phenylmagnesium bromide to methyl β-vinylacrylate and obtained exclusively (75 %) 1,3-diphenylpent-4-en-1-one as the result of one 1,2- and one 1,4-addition (*cf.* VI, above). With methyl cinnamylidenemalonate and phenylmagnesium bromide Reimer [2] found only 1,4-addition, and the same was the case in the reaction of ethyl cinnamylidenecyanoacetate with phenyl- and ethylmagnesium bromides [3]. The methyl ester of α-phenyl-cinnamylideneacetic acid did only with difficulty react at all and gave phenyl 1,2,4-triphenylbut-3- enyl ketone as the result of one 1,2- and one 1,4-addition [4]. Kohler [5] also reports the exclusive 1,4-addition of phenylmagnesium bromide (and benzylmagnesium chloride) to cinnamylideneacetophenone, and Fuson and Libby [6] find that the additions of phenylmagnesium bromide to sorbomesitylene and to sorbodurene take place as 1,4-additions only.

If the β-carbon atom is substituted so as to form a hindrance to 1,4-addition, only 1,2-addition takes place: methyl β-phenyl-cinnamylideneacetate thus gives the tertiary alcohol (1,1,3,5-tetraphenylpenta-2,4-dien-1-ol) with phenylmagnesium bromide [1].

1,6-Additions of Grignard reagents have been described in more special cases [7]. Thus Fuson *et al.*[8] describe the *para*-substitution by Grignard alkyls in the phenyl ring of phenyl duryl ketone and similar sterically hindered ketones. Here the 1,6-addition is followed by the loss of a molecule of hydrogen. Julian *et al.*[9] report the 1,6-addition to certain methylenequinones, *e.g.* methyleneanthrone and fuchsone, resulting in the creation of aromaticity in the rings. In no case, however, has 1,6-addition been observed in a simple linear diene-carbonyl system.

With other nucleophilic reagents, on the other hand, such as the anions of malonic, cyanoacetic and acetoacetic esters, additions take place predominantly as 1,6-additions [10]. Thus the δ-substituted compounds are formed from sorbic and β-vinylacrylic esters [1,11], *e.g.*

$$CH_3CH=CH-CH=CH-COOCH_3 + CH_2(COOCH_3)_2 \xrightarrow{NaOCH_3} CH_3CH(CH(COOCH_3)_2)-CH=CH-CH_2COOCH_3$$

Table 1. Additions of *n*-butylmagnesium bromide to *sec*-butyl sorbate.

Catalyst	Type of products	Yield %		Type of conjugate addition % of total [a]		
		0.1 mole scale	0.2 mole scale	1,4	1,6-(α,δ)	1,6-(γ,δ)
None	conj. add.	40	30	73—75	7—7	20—18
	1,2-add. + conj. add.	20	30	>95	trace	trace
	condensation + conj. add.		0			
CuCl-catalyzed, one portion	conj. add.	52—58	30—35[b]	3—8	24—21	73—71
	1,2-add. + conj. add.	0	0			
	condensation + conj. add.	+	20			
CuCl-catalyzed, step-wise addition	conj. add.	72	72	2	24	74
	1,2-add. + conj. add.	0	0			
	condensation + conj. add.	+	+			

[a] The figures are roughly estimated accurate to the nearest 0.5, 2 and 5 % for the values: below 10 %, around 20 % and 70 %, respectively. Two figures in a column represent results from two determinations.

[b] The ratios between the isomers given are those for 0.1 mole runs only.

although some 1,4-addition occurs as well (in the above reaction to an extent of 7—10 %[12]) depending on the possible presence of substituent alkyl groups at the carbon atoms α,β, and γ[13,14]; thus γ-methylsorbic ester gives 75 % 1,4-addition of ethyl cyanoacetate. The addition of ethyl acetoacetate to sorbic ester has been reported to give high yield of 1,6-addition product, although the possibility that small amounts of 1,4-addition product have been formed can not be excluded [15]. It should be noted that in these cases of 1,6-additions the 1,6-adducts have been reported to be of the type V, that is the β,γ-unsaturated ester.

The analogous reaction of 1-cyanobuta-1,3-diene, which is the "vinylog" of acrylonitrile, has likewise been described to give 1,6-addition of active hydrogen compound [16]. In this reaction, which is analogous to the cyanoethylation, the yields are low, and the possibility of 1,4-addition is not considered by the authors.

Summarizing, it appears as if conjugate additions to an unhindered 2,4-dienic carbonyl compound take place essentially as 1,6-additions when the addends are sodium derivatives of active hydrogen compounds, whereas essentially 1,4-addition occurs when the addends are Grignard reagents.

The present paper describes additions of *n*-butylmagnesium bromide to *sec*-butyl sorbate under conditions which have previously been found favour-

able for conjugate addition [17–19]. The addition products have been subjected to identification work in order to solve the question of 1,4-*versus* 1,6-addition. The effect of cuprous chloride on the course of the addition has been investigated. Also the possible formation of two types of 1,6-addition products (IV and V, above) has been touched upon. The results are summarized in Table 1.

By the uncatalyzed addition of *n*-butylmagnesium bromide to *sec*-butyl sorbate a fair yield of a product was obtained, which distilled within a rather narrow boiling point range, but showed a greatly fluctuating refractive index. This fraction was found to be a mixture of addition products, and by saponification it could be separated in an acidic and a somewhat smaller non-acidic fraction; both of these fractions gave products with sharp boiling points and refractive indices (but the occurrence of a smaller, somewhat higher boiling fraction was noted in each case). Microanalyses of samples of the constant boiling fractions were consistent with the calculated values for a *n*-butylhexenoic acid and a *n*-butyl *n*-butylpentenyl ketone, respectively. The acid is the result of a simple conjugate addition of the Grignard reagent to one double bond of the unsaturated ester, while the ketone is the product of one 1,2-addition (to the ester carbonyl group) and one conjugate addition.

The ketonic product was found (as described below) to be essentially one single isomer, namely the 1,2 + 1,4-addition product (VI).

The acidic product was identified (as described below) as a mixture of about 75 % 1,4-addition product (type III): 3-propenylheptanoic acid and 25 % 1,6-addition products (types IV and V): 5-methylnon-3- and -2-enoic acids.

$$\underset{\text{1,4-adduct: acid}_{III}}{CH_3CH=CH-\underset{C_4H_9}{\underset{|}{CH}}-CH_2COOH}$$

$$\underset{\text{1,6-}(\alpha,\delta)\text{-adduct: acid}_{IV}}{CH_3\underset{C_4H_9}{\underset{|}{CH}}-CH=CH-CH_2COOH} \qquad \underset{\text{1,6-}(\gamma,\delta)\text{-adduct: acid}_{V}}{CH_3\underset{C_4H_9}{\underset{|}{CH}}-CH_2CH=CH-COOH} \qquad (1)$$

The ratios between the two 1,6-adducts were approximately 3 to 1, the α,β-unsaturated acid$_V$ being the one present in the larger amount.

In the cuprous chloride catalyzed reactions the yields of conjugate addition products were considerably better and no ketonic product was obtained. Here the favourable effect of stepwise addition of the cuprous chloride recently found [19] (p. 271) is very pronounced. Furthermore, in the one-portion cuprous chloride catalyzed reaction the yield was much lower when the reaction was run on a larger scale. The dependency on the scale of the run was not found when the cuprous chloride was added in smaller portions concurrently with the addition of the ester. This result is consistent with the view [19] that cuprous chloride is active only for a short period in the Grignard reagent solution. The primarily formed cuprous alkyl (RCu, *cf.* below) will gradually decompose into copper metal and hydrocarbon (R—R), and since the addition time for the ester has to be proportional with the scale of the run [20], the catalyst added in the start is probably only active during the addition of the first minor part of the ester.

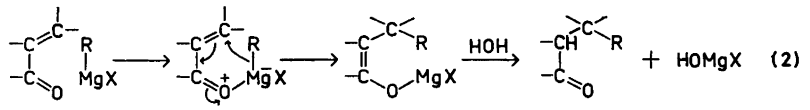
As may be seen from Table 1 some effect of the scale of the run has also been encountered in the uncatalyzed reaction.

In the catalyzed reactions a higher-boiling product was formed. It was only estimated and isolated in one case. It showed the correct analysis for an ester of a dibasic acid, analogous to the high-boiling glutaric esters formed as by-products from crotonic and other esters [20] by a primary intermolecular Michael condensation, leading to a dimer, followed by a conjugate addition. The infra-red spectrum showed the characteristic absorption for *sec*-butyl esters [21], but the product was not further investigated.

The composition of the acid mixture from the cuprous chloride catalyzed reactions was found (see below) to be remarkably different from that encountered in the uncatalyzed reaction. In this case the product to an extent of more than 90 % was the 1,6-addition products, the ratio of which still was: γ,δ-adduct to α,δ-adduct approximately 3 to 1. Less than 10 % of 1,4-addition product was apparently formed.

DISCUSSION

Apart from substituent influences, such as steric, polarization and hyperconjugation effects, which are considered absent in the diene system of sorbic ester *, two factors seem to be important for the competition between 1,4- and 1,6-additions. In a freely conducting, linear conjugated system polarity is most strongly developed at the ends of the system [14]. Since the reaction consists in an attack by a nucleophilic reagent on a positively charged carbon atom, this terminal polarization will obviously favour 1,6-addition to sorbic ester. On the other hand, if the nucleophilic reagent is one like the Grignard reagent, the magnesium atom of which is known to have a fairly strong tendency for coordination with the oxygen of the carbonyl group, a mechanism involving a cyclic, synchronous electron shift should be energetically favourable. Such a mechanism has been proposed by Lutz and Reveley [22] for the conjugate addition of Grignard reagents to α,β-unsaturated systems, and it has been discussed in previous communications of this series [21,23]:



This mechanism involves an electron shift within a *six*-membered ring, and the preference for it will thus favour 1,4-addition over 1,6-addition, which could only arise from a similar mechanism within a sterically much less favourable *eight*-membered ring.

The addition of the sodium derivatives of active hydrogen compounds are examples of the Michael addition reaction. As discussed by Ingold [14], this is a reversible process, which in the cases reported has most likely been run to

* That this is not strictly true is shown by the above cited 7 – 10 % 1,4-Michael addition actually observed in the case of sorbic ester, in contrast to the case of β-vinylacrylic ester which gives exclusively 1,6-addition [1,11,12].

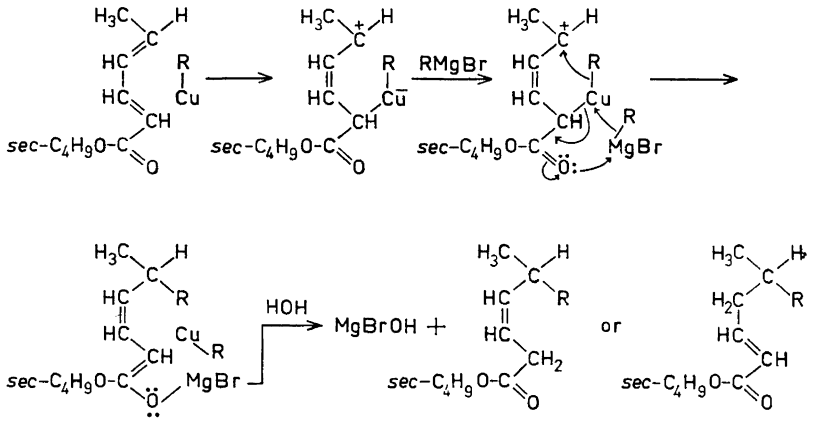
equilibrium, and the resulting addition is therefore probably thermodynamically controlled. This may in most cases, including that of sorbic ester, account for the above-mentioned reported additions.

On the other hand the addition of a Grignard reagent is probably kinetically controlled, and here, although the terminal polarization will favour 1,6-addition, the operation of the cyclic mechanism readily accounts for the predominance of 1,4-addition of Grignard reagents. The results with sorbic ester in the uncatalyzed reaction thus lends further support to the cyclic mechanism.

Cuprous chloride catalysis. As to the effect of cuprous chloride to cause the drastic change in orientation, two viewpoints could be put forward. The generally experienced effect (also found in the work here described) of this catalyst to promote conjugate addition over 1,2-addition in α,β-unsaturated systems [18,24] could be ascribed to a tendency of the cuprous ion to coordinate with the double bond, thus making this more vulnerable for attack of nucleophilic reagents by increasing its polarization (*cf.* below). One would expect that the carbon atom with which the cuprous ion should preferably coordinate would be the α-carbon, and in the case of the diene system the result might then be an increase of the polarization through the full conjugated system; thus the fractional positive charge at the terminal δ-carbon atom should increase. Furthermore, it must be assumed [25] that the cuprous chloride, when added to the Grignard solution, will react to form the cuprous alkyl:

$$\mathrm{RMgBr} + \mathrm{CuCl} \longrightarrow \mathrm{MgBrCl} + \mathrm{RCu}$$

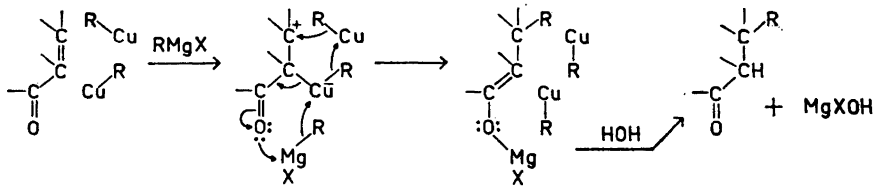
which will then coordinate with the alkenic carbon; thus the following cyclic mechanism, leading to 1,6-addition (and involving a *six*-membered ring) is rendered possible [26]:



This mechanism accounts for the change in orientation of conjugate addition by the presence of cuprous chloride, and it is consistent with the previously suggested mode of action for cuprous chloride in promoting reduction

of the carbon-carbon double bond in citraconic and mesaconic esters by means of *n*-butylmagnesium bromide [21].

It should be mentioned that a similar cyclic mechanism, involving *two* molecules of cuprous alkyl, one of which coordinates with the α-carbon atom, could explain the above-mentioned *general* effect of cuprous chloride to catalyze the conjugate addition in competition with the 1,2-addition [18,21,24] and the condensation-addition process [20,19]:



This mechanism is analogous to that suggested by Swain and Boyles [27] for the addition of Grignard reagents to carbonyl groups. In this way all known effects of cuprous chloride on Grignard reactions with α,β-unsaturated esters could be accounted for on the same basis, *viz.* the concept of cuprous ion-alkene carbon coordination.

However, this mechanism implies that the tendency to addition of the cuprous alkyl to the carbon-carbon unsaturated system is greater than for the alkylmagnesium bromide to add to the carbonyl group. Although Gilman has stated [28] that alkylmagnesium halides are more reactive towards addition to carbonyl groups than are cuprous alkyls, it must be remembered that in the case of α,β-unsaturated carbonyl compounds the reactivity of the carbonyl group is strongly reduced by the conjugation with the double bond, and, conversely, the electrophilic reactivity of the β-carbon atom of the double bond correspondingly enhanced. Thus Gilman's reactivity sequence is not likely to be valid in this case. On the contrary, it could be considered as a reasonable assumption that cuprous alkyls are more reactive than Grignard reagents towards addition to an α,β-unsaturated carbonyl compound.

The question of the relative amounts of the two 1,6-adducts [28a] has not really been considered, since the ratio between them should be dependent on the course of the secondarily occurring tautomerization only. Furthermore, the possibility of migration of the double bond during the saponification could not be entirely excluded, although, apparently such a transformation is not encountered in the case of the 1,4-adduct. The infrared spectrum of the adduct-ester from the cuprous chloride catalyzed addition did not show the absorption characteristic for conjugated carbon-carbon double bonds (1 600—1 650 cm^{-1}) as did the spectrum of the acid obtained from it (*cf.* Table 2), and the ester carbonyl band (1 740 cm^{-1}) was found above the region usually assigned to α,β-unsaturated ester carbonyl (1 730—1 717 cm^{-1}). These facts, however, do not necessarily exclude the possibility that the ester also is α,β-unsaturated [29].

The questions of the composition of the ketonic adduct obtained in the uncatalyzed reaction and of the non-formation of such a ketonic adduct in the cuprous chloride catalyzed reaction are considered in the experimental part.

IDENTIFICATION AND ESTIMATION OF ISOMERIC ACIDS

This was accomplished by means of gas-liquid chromatography and infra-red spectroscopy (besides conventional chemical analytical methods). The problem was attacked in two ways: investigation of the mixture of unsaturated acids obtained by saponification of the primary products (*cf.* Table 2), and investigation of saturated acids produced by the oxidative degradation of the unsaturated acids.

Identification of unsaturated acids. By fractional distillation the mixtures of acids could be separated in only two fractions, one boiling at 98—99°/0.6 mm and one at 110—110.5°/0.7 mm, both fractions giving correct analyses for $C_{10}H_{18}O_2$. The product from the uncatalyzed addition process consisted almost exclusively of the low-boiling acid.

Infra-red spectroscopy indicated a double bond in the α,β-position to the carboxyl group [29a] in the secound of these fractions, whereas this conjugation was absent in the first fraction.

Table 2. C_{10}-Acids from adducts and authentic samples. Physical data and analyses. (Calc. for $C_{10}H_{18}O_2$ (170.24): C 70.54; H 10.66; neutr. equiv. 170.24).

Acid	b.p. °C/mm Hg	Ref. index at °C	Analyses	Infra-red spectrum
No. 1. from non-cat. addition	98—101/0.7 118—121/3	1.4462 at 25° 1.4494 at 20°	neutr. equiv. 172	similar to those of nos. 2, 4 and 5
No. 2. low-boil. from CuCl-cat. addition	98—99/0.6	1.4485 at 20°	C 70.65 H 10.60	similar to those of nos. 1, 4 and 5
No. 3. high-boil. from CuCl-cat. addition	110—110.5/0.7	1.4623 at 20°	C 70.45 H 10.66	similar to that of no. 6, bands at 1 707 cm^{-1}(C=O) and 1 655 cm^{-1} (C=C)[a]
No. 4. authentic $acid_{III}$ (mixture[b])	92/0.5	1.4471 at 20°	C 70.55 H 10.49	similar to those of nos. 1, 2 and 5
No. 5. authentic $acid_{IV}$	102/1	1.4481 at 20°	C 70.35 H 10.63	similar to those of nos. 1, 2 and 4
No. 6. authentic $acid_{V}$	110—111/0.9	1.4610 at 25°	C 70.45 H 10.46	similar to that of no. 3.

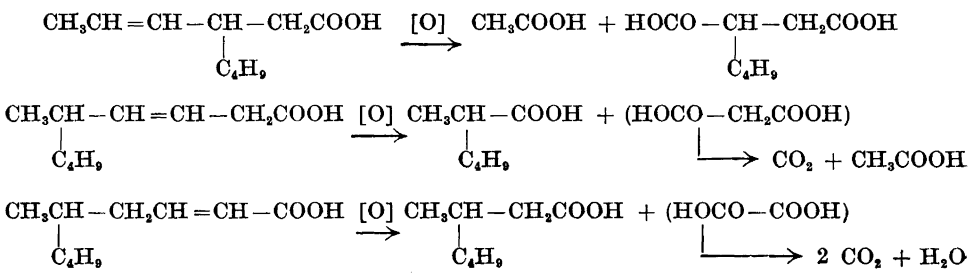
[a] Characteristic absorptions for α,β-unsaturated acids [29a].
[b] See experimental part, p. 288.

The three possible isomeric acids: $acid_{III}$, $acid_{IV}$ and $acid_{V}$ (*cf.* (1), p. 280) were synthesized independently by other routes, as described below. Of these (*cf.* Table 2), acid III (the 1,4-adduct) and $acid_{IV}$ (the 1,6-(α,δ)-adduct) had very similar physical properties (boiling points, refractive indices and infra-red spectra), and these properties were largely in agreement with those of the lower-boiling acid-fraction obtained by the addition reactions. The properties of the higher-boiling acid-fraction, on the other hand, were very nearly the same as those of the authentic 1,6-(γ,δ)-adduct ($acid_{V}$).

By gas chromatography, however, the acids from the addition reactions were further separated, and *the components were identified* as $acid_{III}$, $acid_{IV}$ and $acid_{V}$ (1). All three isomeric acids were found in both the above-mentioned fractions. The lower-boiling fractions (from the uncatalyzed as well as from the catalyzed addition) were, essentially, mixtures of acid III and acid IV, whereas the higher-boiling fraction (from the catalyzed reaction only) was practically pure $acid_{V}$.

In order to *estimate the ratios of isomeric adducts* in the products, the two addition reactions were repeated twice and, after saponification, the crude acidic reaction products were analyzed gas-chromatographically, giving, in average, the results of Table 1.

Further evidence of the *identities* of the acid-isomers was obtained by oxidative degradation with alkaline potassium permanganate. By this treatment the three isomers should give, as main products, *n*-butylsuccinic acid, 2-methylhexanoic acid and 3-methylheptanoic acid, respectively:



These three acids were synthesized independently as authentic samples (see experimental part), and by gas-chromatographic investigation the oxidation products were found to be, essentially, mixtures of them. *n*-Butylsuccinic acid, which is a solid (m.p. 81°), was isolated analytically pure, and it was further identified by comparison with the authentic sample, also with respect to infra-red spectrum and mixed melting point.

The ketonic product from the uncatalyzed reaction appears, according to the gas-chromatographic analysis, to contain only one compound. The infra-red spectrum showed a ketonic carbonyl group but no indication of conjugated carbon-carbon double bond. This ketone was identified as the 1,2 + 1,4-addition product (VI) by comparison of its data with those of ketonic samples synthesized from the acidic addition products. However, this does not necessarily mean that only this kind of 1,2 + conjugate addition occurs (see experimental part).

GAS-LIQUID CHROMATOGRAPHIC IDENTIFICATIONS AND DETERMINATIONS

The instrument used was a Griffin and George apparatus, mark II.

The acids were separated as the methyl esters into which they were converted by treatment for 5 min. with a 2 % solution of diazomethane in ether, followed by evaporation of the excess of diazomethane and ether on the steam-bath [30]. The column consisted of 1.8 m of Celite 545 with 25 % of "Apiezon" grease M. Helium was used as the carrier gas with a flow rate of 1 l per h. The operating temperature was 160° and the sample size was 10—20 mg.

In the case of the ketonic products the column consisted of 0.9 m of Celite 545 with 30 % of silicone elastomer E 301. The operating temperature was 180° while the other conditions were the same as those for the methyl esters.

The retention times are given in Table 3.

The quantitative determinations are based upon the assumption that the areas under the recorded peaks are proportional to the molar percentages of the corresponding components in the mixtures. Previously, quantitative analyses of methyl esters of *straight chain* fatty acids [31] have indicated that, by using this principle of calculation, the values obtained for the components being present in large quantities may be somewhat too high. Such an uncertainty may be eliminated by calibrating the instrument on pure compounds. Although the error thus introduced is unknown in the present case, it is probably small and certainly not of major importance for the problems under discussion in this work. No attempt has, therefore, been made to calibrate the instrument with respect to the components analyzed.

EXPERIMENTAL

Microanalyses are by Mr. Preben Hansen, Microanalytical Division, The Chemical Laboratory, The University of Copenhagen. Fractional distillations were through a simple 45 cm × 8 mm Podbielniak-type coloumn with a tantalum wire spiral, a heated jacket and a partial reflux head.

All products were checked by infra-red spectroscopy on solutions in carbon tetrachloride, using a Beckman IR2 single-beam spectrophotometer with sodium chloride optics. The spectra were recorded by one of us (S.R.) except for the spectra of acid$_{IV}$, ketone$_{none}$ and ketone$_{CuCl}$, which were measured by Mrs. Inger Grete Krogh Andersen, M.Sc.

Table 3. Gas-liquid chromatographic retention times (min) for addition products.

Type of product	Type of adduct		
	1,4	1,6-(α,δ)	1,6-(γ,δ)
Methyl ester of acid	31	37	61
Ketone	26	29	47

sec-*Butyl sorbate was prepared* from commercial acid (Fluka, *purum*) using the general esterification procedure previously described [20], b.p. 105°/17 mm, n_{20}^{D} 1.4846, yield 85 %. (Neutr.equiv. found: 167.6. Calc. for $C_{10}H_{16}O_2$: 168.23).

Non-catalyzed additions of n-*butylmagnesium bromide to* sec-*butyl sorbate* were carried out in 0.1 or 0.2 mole scales as previously described [17]: The solution of *n*-butylmagnesium bromide was prepared during about 1 h from 12.6 g (0.52 g-atom) of magnesium and 85 g (0.62 mole) of *n*-butyl bromide dissolved in 240 ml of ether. The solution was effectively stirred and cooled in ice-water during 15 min; then 33.6 g (0.2 mole) of *sec*-butyl sorbate, dissolved in 200 ml of ether, was added dropwise over a period of about 3 h. When the addition was completed, stirring was continued in the ice-bath for another 15 min and for 1 h at room temperature. The reaction mixture was then poured onto a mixture of ice, concentrated hydrochloric acid (55 ml) and ether (100 ml) under vigorous shaking and worked up the conventional way [20]. When only 0.1 mole of ester was used the addition time was about 1.5 h.

The fractional distillations gave, in 65 % yield, a product with boiling point range 77—101°/0.7 mm and refractive index range n_D^{25} 1.4426—1.4767. Most of this product (75 %) distilled at 77—82°/0.7 mm and had n_D^{25} 1.4430, but showed by elementary analysis the carbon content too high for the simple conjugate addition product. This product, on saponification (see below), gave a 50 % yield of an acid (compound 1, Table 2). In addition a 35 % yield of a non-acidic ketonic product, b.p. 85—86°/1 mm, n_D^{20} 1.4500, was obtained. (Found: C 79.90; H 12.40. Calc. for $C_{14}H_{26}O$ (210.35): C 79.93; H 12.46).

Cuprous chloride catalyzed addition of n-*butylmagnesium bromide to* sec-*butyl sorbate* differed from the non-catalyzed addition in that 1.5 mole per cent of cuprous chloride * was added to the Grignard reagent after cooling in ice-water for 15 min, either in one portion just before addition of the ester is started [18] or in small portions at intervals of 20—30 min throughout the addition of the ester solution [19].

By the distillation was obtained a mixture of simple conjugate addition products: *sec*-butyl *n*-butylhexenoates (III, IV and V), b.p. 82°/0.9 mm, n_D^{25} 1.4383. (Found: C 74.40; H 11.47. Calc. for $C_{14}H_{26}O_2$ (226.25): C 74.28; H 11.58). A higher-boiling fraction, b.p. 151—154°/0.9 mm, n_D^{25} 1.4622, is probably a condensation-addition product (*cf.* above, p. 281). (Found: C 72.80; H 10.38. Calc. for $C_{24}H_{42}O_4$ (394.58): C 73.05; H 10.73).

The lower-boiling ester-mixture was saponified (see below). No non-acidic fraction was found (*cf.* below). The acidic fraction distilled over a long boiling point range. By careful fractionation two samples were obtained: a low-boiling fraction (compound 2, Table 2) and a high-boiling fraction (compound 3, Table 2).

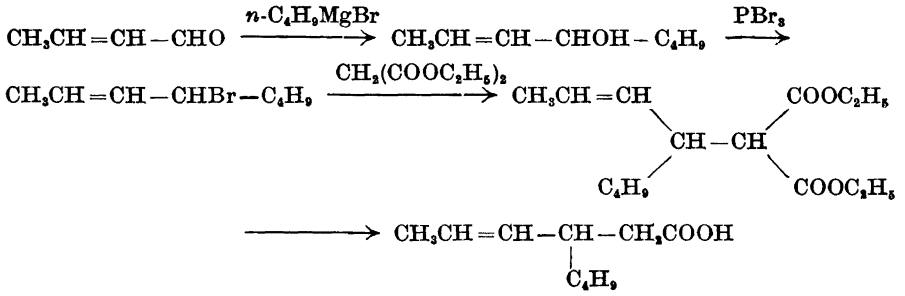
Saponifications of esters were carried out essentially as previously described [20]: The ester, dissolved in ethanol was refluxed with a three-fold excess of potassium hydroxide for at least 8 h. The ethanol, 2-butanol and other non-acidic products were removed by distillation and extraction, and the acidic products were then obtained by acidification and extraction.

Preparation of authentic adduct-acids. For the use in the gas-chromatographic and spectroscopic identification work (above) the acids corresponding to the three types of adducts (III, IV and V) were prepared ** as authentic samples (see Table 2). Of these, $acid_{III}$, 3-propenylheptanoic acid (compound 4, Table 2) was prepared by the malonic ester synthesis from 4-bromoöct-2-ene. This "allylic" bromide was obtained by the action of phosphorus tribromide on the

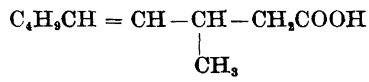
* With respect to the Grignard reagent, *e.g.* 0.75 g of cuprous chloride to 0.2 mole of ester.

** The valuable participation in this synthetic work by Mr. Henrik Brink Clausen, Miss Jette Holmblad, Mr. Steffen Jacobsen, Mr. Axel Sonne and Mr. Peter Tommerup, students at the Polyteknisk Læreanstalt for the M.Sc. degree in chemical engineering, is gratefully acknowledged.

corresponding alcohol, prepared from crotonaldehyde and *n*-butylmagnesium bromide *:



It was expected that this acid$_{III}$-sample should be a mixture of this acid and the isomeric 3-methylnon-4-enoic acid, resulting from an allylic inversion at one of the steps above:



This mixture should, however, be just as useful for the identification by gas chromatography as the pure acid $_{III}$. This proved also to be the case. The product was found to contain about 50 % of acid$_{III}$, which was easily recognized, but the remainder consisted of not one, but two isomeric acids amounting to about 20 and 30 %, resp., of the mixture.

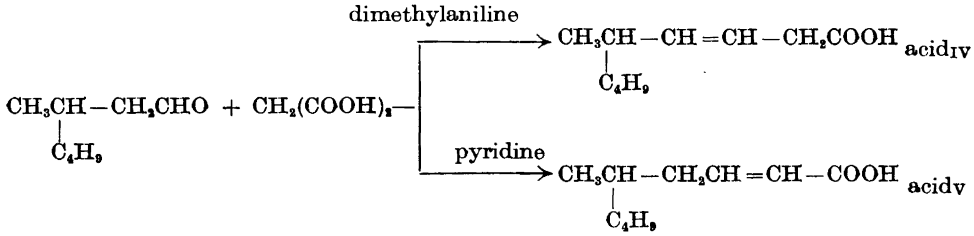
The following data was found for the intermediate compounds. The alcohol, oct-2-en-4-ol, was prepared in 65 % yield according to Hurd and Puterbaugh [32a], b.p. 77–80°/13 mm, n_D^{20} 1.4417 (rep.[32a] 74°/8 mm, n_D^{20} 1.4395). The gas-chromatographic analysis indicated a mixture of two compounds, but the amount of one of them was only about 15 %. The bromide, 4-bromoöct-2-ene, was obtained in about 45 % yield using a procedure given by Jones *et al.*[33] for methallyl bromide; b.p. 67–69°/10 mm, n_D^{25} 1.4631 (rep.[34] b.p. 76°/18 mm, n_D^{25} 1.4632). The gas-chromatographic analysis indicated the presence of two bromides, representing about 15 and 85 %, resp., of total. The alkylated malonic ester, diethyl 2-propenylhexan-1,1-dicarboxylate, was prepared in 52 % yield as described for *n*-butylmalonic ester in *Organic Syntheses* [35], b.p. 98–100°/0.6 mm, n_D^{25} 1.4422. (Found: C 66.70; H 9.56. Calc. for $C_{15}H_{26}O_4$ (270.36): C 66.63; H 9.69). The gas-chromatographic analysis showed the presence of three compounds, the percentages being approximately 40, 45 and 15 %, resp. The last step in the above sequence, the hydrolysis and decarboxylation of the malonic ester, was carried out essentially as described in *Organic Syntheses* for 3-methylpentanoic acid [36]. However, decarboxylation did not take place as readily as there indicated, and, consequently the acid distilled off only very slowly. The crude reaction mixture (probably mainly un-decarboxylated malonic acid) was

* This sequence of reactions were suggested to us by the analogous preparation of 3-methylhex-4-enoic acid [32] by Jack W. Ralls and William J. Weston of United States Department of Agriculture, Agricultural Research Service, Western Utilization and Development Division, Albany 10, California. This information was kindly placed at our disposal by Dr. Jack W. Ralls, who reports the preparation in high purity of methyl 3-methylhex-4-enoate in an overall yield of 56 % from the corresponding alkylated malonic ester, which in turn was obtained in 84 % yield. The methyl 3-methylhex-4-enoate was found by gas chromatography to consist of one single compound.

subjected to distillation *in vacuo*. Now decarboxylation did take place, and a crude acid, b.p. 140°/20 mm, was obtained. After redistillation (*cf.* Table 2) the yield of $acid_{III}$ was 69 %.

The problem of the identities of the isomers in the malonic ester and the $acid_{III}$ preparation has not yet been solved but is the subject of further studies.

$Acid_{IV}$ and $acid_V$ were both obtained by the condensation of 3-methylheptaldehyde with malonic acid:



The use of pyridine, according to the general procedure given in *Organic Syntheses* [37], leads to the predominant formation of the α,β-unsaturated $acid_V$, whereas the use of other amine bases, such as dimethylaniline, according to Boxer and Linstead [38], gives the β,γ-unsaturated $acid_{IV}$.

The 3-methylheptaldehyde, b.p. 50—52°/10 mm, was secured in 40 % yield by the Rosenmund reduction [39] of the acid chloride. Toluene was used as the solvent instead of xylene in order to facilitate separation of the aldehyde by fractional distillation. 3-Methylheptanoyl chloride, b.p. 70—72°/10 mm, was obtained in about 90 % yield from the acid by means of thionyl chloride. The preparation of 3-methylheptanoic acid (*cf.* below) is previously described [20].

Preparation of authentic adduct-ketones. The corresponding authentic ketones proved considerably more difficult to obtain. After several unsuccessful attempts to synthesize them along independent routes, two ketonic samples were prepared using the acid-mixtures from the adducts as starting materials: the lower-boiling acid from the uncatalyzed addition reaction (compound 1, Table 2; mainly the 1,4-adduct) and the acid-mixture from the cuprous chloride catalyzed reaction (compounds 2 + 3, Table 2; essentially 1,6-adducts). These acid-mixtures were converted into the crude acid chlorides (b.p. 95—105°/15 mm and 73—80°/1.2 mm, resp.) in 80—90 % yields by treatment with thionyl chloride at room temperature for several hours. From the acid chlorides the crude *n*-butyl ketones were prepared (in yields of 68 and 35 %, resp.) using the cadmium reaction as described by Cason [40]: The acid chloride, dissolved in benzene, was added to di-*n*-butylcadmium in benzene, prepared from *n*-butylmagnesium bromide and dry cadmium chloride.

Purified samples of the two ketones showed the following physical data (calc. for $C_{14}H_{26}O$ (210.35): C 79.93; H 12.46):

$Ketone_{none}$ (from the "non-catalyzed adduct-acid mixture"), b.p. 81—83°/0.7 mm, n_D^{25} 1.4444. (Found: C 79.95; H 12.60.)

$Ketone_{CuCl}$ (from the "cuprous chloride catalyzed adduct-acid mixture"), b.p. 89—92°/0.5 mm, n_D^{25} 1.4492. (Found: C 78.20; H 12.23.)

Comparison of their infra-red spectra with the spectrum of the ketonic product, obtained directly by the addition reaction, indicated this ketone to be identical with $ketone_{none}$, that is the 1,2 + 1,4-addition product VI. Whereas this compound did not show infra-red absorption characteristic for an α,β-unsaturated ketone (the C=O band being at 1 715 cm^{-1}), this was indeed the case with $ketone_{CuCl}$, which showed a split C=O absorption with peaks at 1 685 and 1 665 cm^{-1} and a strong C=C band at 1 610 cm^{-1} [41].

The gas-chromatographic analyses of the two ketonic samples indicated $ketone_{none}$ to be essentially one single compound, identical with the ketonic adduct. $Ketone_{CuCl}$, on the other hand, contained two compounds, of which the one present in the smaller quantity (about 15 %) was identical with $ketone_{none}$ (and the ketonic adduct), whereas the one present in the larger amount (about 85 %) had a longer retention time (*cf.* Table 3).

$Ketone_{CuCl}$ was obtained only in a poor yield, a large amount of non-distillable polymeric products being formed. As the elementary analysis (above) showed, the product is not pure. However the infra-red spectrum and the gas-chromatographic analysis indicated that it is essentially the α,β-unsaturated 1,6-(γ,δ)-ketone, as expected since it is obtained from an acid-product consisting mainly of the corresponding unsaturated acid. Several attempts were made to purify $ketone_{CuCl}$ in order to obtain a sample showing the correct elementary analysis. Each time the major part of the product was lost because of extensive polymerization. The instability of the α,β-unsaturated ketone towards polymerization not only explains the low yield and purity of $ketone_{CuCl}$, but also the fact that $ketone_{CuCl}$ contains as much as 15 % of the 1,4-ketone (VI) while the acid from which it is made only contains a few percent of 1,4-acid ($acid_{III}$). Likewise, the $ketone_{none}$ is almost 100 % 1,4-ketone (VI) while the acid mixture from which this ketone is derived contains 20 % of α,β-unsaturated acid ($acid_V$). In fact, the easy polymerization of the α,β-unsaturated ketone under alkaline conditions is probably also the reason for the two encountered results: a) the ketone obtained in the uncatalyzed reaction is almost 100 % 1,4-ketone (VI) in contrast to the corresponding acid-adduct which contains as much as 20 % of α,β-unsaturated acid ($acid_V$), and b) no ketonic adduct whatsoever is obtained in the cuprous chloride catalyzed reaction, although it would indeed have been reasonable to expect at least some 1,6-ketone. The latter may very well form, however, but one would expect it to be mainly the α,β-unsaturated ketone, which will polymerize. Thus the percentages given in Table 1 for the ketonic adducts do probably not give the true picture of the 1,2 + conjugate additions which have actually taken place.

Oxidative cleavage. Unsaturated acids were oxidized essentially according to the procedure of *Organic Syntheses* [42] for the preparation of azelaic acid from castor oil. In a 2 l three-necked flask, fitted with mechanical stirring, 98 g (0.62 mole) of potassium permanganate was dissolved in 1 200 ml of water. The solution was heated to 35°, and 20 g (0.118 mole) of unsaturated acid, dissolved in a solution of 10 g (0.18 mole) of potassium hydroxide in 250 ml of water, was added in one portion. In 5 min the temperature rose to 60—65° and stayed there for about 1 h. The reaction mixture was now subject to filtration which was very slow (several hours), and the manganese dioxide was washed twice with hot water. The alkaline solution was evaporated to about 750 ml, and, after acidification, continuously extracted with ether for 24 h. The ether solution was dried over sodium sulfate, and the ether and most of the acetic acid (*cf.* p. 285) was distilled. The residue was subjected to gas-liquid chromatography, and the components: *n*-butyl-

succinic, 2-methylhexanoic, and 3-methylheptanoic acids were identified by comparison of the retention times with those of the authentic samples described below.

In the case of the acid-fraction from the uncatalyzed reaction, the residue solidified and a 65 % yield of *n*- butylsuccinic acid was obtained. However, by the gas-chromatographic analysis 2-methylhexanoic and 3-methylheptanoic acids were found as well. In the case of the acid-product from the cuprous chloride catalyzed reaction *n*-butylsuccinic acid crystallized in the otherwise liquid residue. Also here all three possible degradation products were found.

Authentic *n-butylsuccinic acid*, m.p. 81°, was obtained by saponification (se above) of its *sec*-butyl ester, which was available from the addition of *n*-butylmagnesium bromide to *sec*-butyl maleate [21]. Authentic *2-methylhexanoic acid*, b.p. 104—105°/15 mm, n_D^{25} 1.4220, neutr. equiv. 132 (calc. for $C_7H_{14}O_2$: 130.18), was prepared by the malonic ester synthesis from diethyl methylmalonate and *n*-butyl bromide according to the procedure of *Organic Syntheses* [35,36]. Authentic *3-methylheptanoic acid*, b.p. 116°/10 mm, was obtained by saponification (se above) of its *sec*-butyl ester, which was available by the addition of *n*-butylmagnesium bromide to *sec*-butyl crotonate [17,19].

Also the *ketone* obtained by the addition process was subjected to oxidative cleavage, ozonization being applied in this case [43]. The crude ozonides were oxidized with peracetic acid, the resulting acid mixture transformed into methyl esters as above [30], and analyzed by gas chromatography. Although no proper identification was attained because of the lack of an authentic sample of the main cleavage product, further evidence for the identity of the ketone with VI was found in the fact that the cleavage product was a large-molecule acid, with a retention time far above those of 2-methylhexanoic and 3-methylheptanoic acids (*cf.* above) which would have been the main cleavage products from 1,2 + 1,6-addition product ketones.

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