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

XV. Reactions with Octa-2,4,6-trienoic Ester. General Discussion of the Conjugate Addition Reaction

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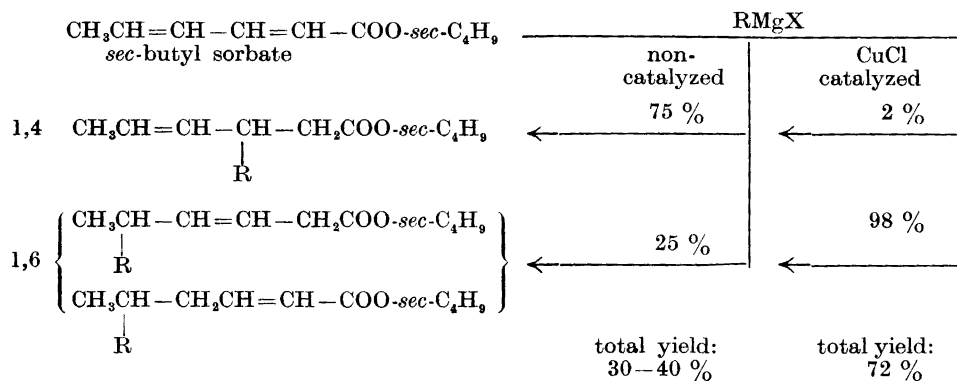*Organisk-Kemisk Laboratorium, Polyteknisk Læreanstalt, Copenhagen, Denmark*

The reaction between butylmagnesium bromide and *sec*-butyl octa-2,4,6-trienoate has been investigated. From the uncatalyzed reaction only traces of simple conjugate addition product can be isolated. About 50 % of the ester undergoes a Michael condensation reaction, and the rest polymerizes. When the reaction is catalyzed by copper(I) chloride, no simple Michael condensation takes place, but a 25 % yield of simple conjugate addition product is obtained, consisting entirely of 1,8-adduct(s). The remainder of the reaction product can not be distilled.

The mechanism of conjugate addition as well as the copper(I) chloride effect are discussed.

Details of the preparation of 3-butyloctanoic, 5-propylnonanoic, and 7-methylundecanoic acids and their *sec*-butyl esters, as well as of a number of intermediates, are given.

Previously the course of reaction between a Grignard reagent and an ester of sorbic (hexa-2,4-dienoic) acid was described.[1] It was found that besides 1,4-addition, expected from the results with similar systems reported by Kohler,[2] some 1,6-addition took place as well. The former addition type was predominant (75 %), however, in the uncatalyzed reaction. In the presence of copper(I) chloride, on the other hand, not only was the total yield of conjugate addition products considerably higher, but the conjugate addition now took place almost entirely as a 1,6-addition:*

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* Throughout this paper the Grignard reagent shall be designated RMgX. For considerations concerning the structure of the Grignard reagent with special references to conjugate addition reactions, two recent papers[3,4], in which further references are given, may be consulted.

$CH_3CH=CH-CH=CH-COO\text{-}sec\text{-}C_4H_9$

sec-butyl sorbate

	RMgX	
	non-catalyzed	CuCl catalyzed
1,4 $CH_3CH=CH-CH-CH_2COO\text{-}sec\text{-}C_4H_9$ $\downarrow$ R	← 75 %	← 2 %
1,6 $\begin{cases} CH_3CH-CH=CH-CH_2COO\text{-}sec\text{-}C_4H_9 \\ \quad \downarrow \\ \quad R \\ CH_3CH-CH_2CH=CH-COO\text{-}sec\text{-}C_4H_9 \\ \quad \downarrow \\ \quad R \end{cases}$	← 25 %	← 98 %
	total yield: 30–40 %	total yield: 72 %

Suggestions as to how these results might be understood were tentatively put forward (*cf.* below). In the corresponding reaction with octa-2,4,6-trienoic ester, described in the sequel, the conjugate addition might take place not only as 1,4- and 1,6-additions, but as 1,8-addition as well. Some insight might therefore be gained into the question whether the 1,6-addition, encountered in the case of sorbic ester, is a sterically or structurally conditioned orientation, specifically directed towards the δ-carbon atom, or whether, in general, the Grignard alkyl enters at that carbon atom, which forms the positive end of a conjugated chain. In the former case, 1,6-addition might be expected to take place also with octatrienoic ester, whereas, in the latter case, 1,8-addition should be favoured (*cf.* eqn. (2)). Unfortunately, however, the predominant reaction, which *sec*-butyl octa-2,4,6-trienoate undergoes in the presence of butylmagnesium bromide, has in all runs been polymerization (or, at any rate, the formation of non-distillable, high-boiling products). The non-catalyzed reaction gave only a trace of simple conjugate addition product, while from the copper(I) chloride catalyzed process a maximum yield of 25 % was obtained. Since, on the other hand, the product obtained in the latter case is exclusively the 1,8-adduct, it seems warranted to give some consideration to the result. Accordingly we shall attempt to reconsider and correlate the previous and present evidence in order to reveal some general features of the reaction.
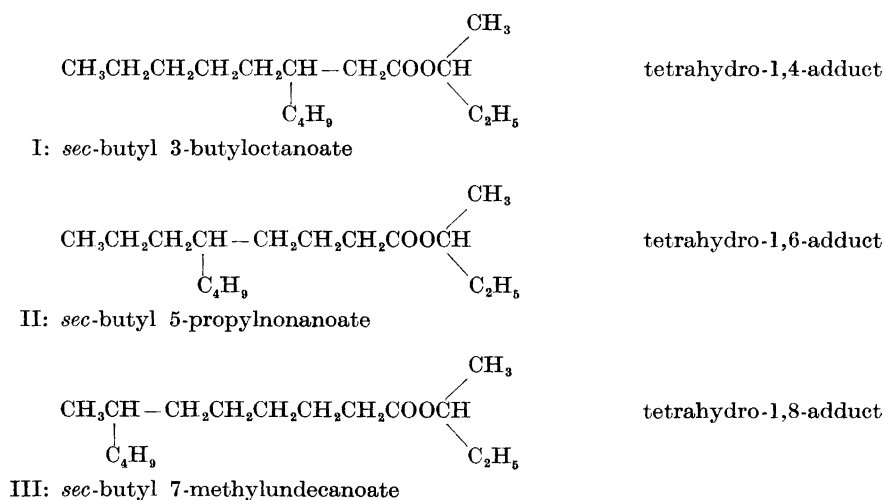
Furthermore, we wish to report on the synthetic work leading to the authentic compounds needed for the identification of the adducts.

In the literature conjugate addition reactions between 2,4,6-trienic carbonyl compounds and nucleophilic reagents are indeed reported. The Michael addition of methyl malonate to methyl octa-2,4,6-trienoate was described by Farmer and Martin,[5] the total yield of adducts being 74 %. Of these the major part (64 %) was the 1,4-adduct, while at least 10 % represented 1,8-addition products. No 1,6-adduct was detected, but its presence could not be excluded. On the other hand, methyl hepta-2,4,6-trienoate has more recently been shown by Acker and Anderson[6] to undergo almost exclusively 1,8-addition with ethyl malonate. This remarkable influence of a terminal methyl group upon the orientation of the addition is consistent with the similar (although less drastic) effect found in the 2,4-dienic system, going from β-vinylacrylic to sorbic ester.[7]

The conjugate addition of ethyl malonate and ethyl cyanoacetate to 5-mesitoylacenaphthylene has been found by Fuson and Mange [9] to take place at the 1-position, a reaction which may be considered as a 1,8-addition. The reaction of this ketone with various Grignard reagents, on the other hand, led to unidentified, probably high-molecular products. Recently, Chapman, Pasto and Griswold [10] have reported the reaction of methylmagnesium bromide with tropone and 4-methoxytropone to give the corresponding 2-methylcycloheptadienones. This reaction could indeed be regarded as a 1,8-addition, although it certainly is a very special case, which should probably be considered as typical of the tropone system rather than of the 2,4,6-trienic carbonyl system.

Reactions between *sec*-butyl octa-2,4,6-trienoate and butylmagnesium bromide

As mentioned above, a well-defined simple conjugate addition product was obtained only in the copper(I) chloride catalyzed addition. A 20—25 % yield of adduct was isolated, analyzing correctly for a butyloctadienoic ester. Disregarding geometrical isomers, six different compounds of this type are, however, conceivable as products of the reaction, *viz.* one 1,4-adduct, two 1,6-adducts, and three 1,8-adducts, the two remaining double bonds occupying different positions. Since these positions, determined by the course of the hydrolysis of the magnesium enolates primarily formed, were not of major significance for the present discussion, no attempts were made to locate them. The reaction product was hydrogenated to the saturated ester(s), thus reducing the number of possible isomeric components in the reaction product to the three tetrahydro-1,4-, 1,6-, and 1,8-adducts, *viz. sec*-butyl octanoate carrying a butyl group as substituent in the 3-, 5- and 7-position, respectively:

$$CH_3CH_2CH_2CH_2CH_2CH-CH_2COOCH \quad \overset{CH_3}{\underset{C_2H_5}{<}}$$
$$\underset{C_4H_9}{|}$$

I: *sec*-butyl 3-butyloctanoate

tetrahydro-1,4-adduct

$$CH_3CH_2CH_2CH-CH_2CH_2CH_2COOCH \quad \overset{CH_3}{\underset{C_2H_5}{<}}$$
$$\underset{C_4H_9}{|}$$

II: *sec*-butyl 5-propylnonanoate

tetrahydro-1,6-adduct

$$CH_3CH-CH_2CH_2CH_2CH_2CH_2COOCH \quad \overset{CH_3}{\underset{C_2H_5}{<}}$$
$$\underset{C_4H_9}{|}$$

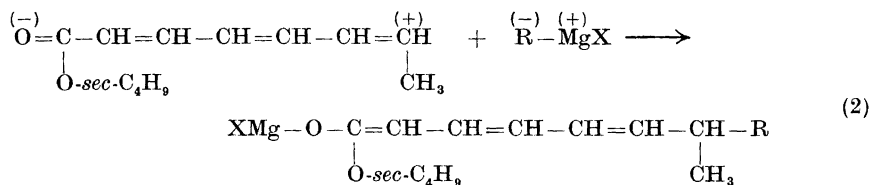III: *sec*-butyl 7-methylundecanoate

tetrahydro-1,8-adduct

Although, according to gas-chromatographic analysis, the conjugate addition product consisted of two components, the hydrogenated product was homogeneous and could be identified as *sec*-butyl 7-methylundecanoate, resulting from 1,8-addition.
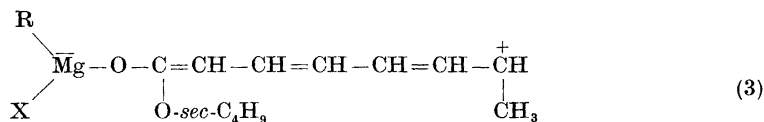
DISCUSSION

Two types of mechanisms can be visualized as operative in the conjugate addition process:* *A*. a cyclic synchronous electron shift within a six-membered ring,[13] discussed in previous communications:[1,3,14]

$$(1)$$
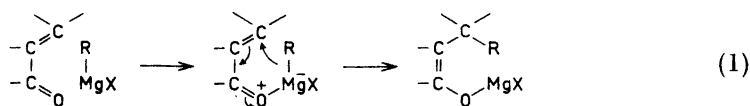
B. a direct carbanion attack by the Grignard reagent alkyl group (either from the Grignard reagent itself or from a complex between it and the ester, *cf.* below) at the positively polarized β-carbon atom. In case of a longer chain of conjugated double bonds the positive charge will be most strongly developed on carbon atoms *delta, zeta etc.* This latter mechanism can schematically be represented as:

$$\overset{(-)}{O}=C-CH=CH-CH=CH-CH=\overset{(+)}{CH} \quad + \quad \overset{(-)}{R}-\overset{(+)}{MgX} \longrightarrow$$
$$\qquad | \qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad |$$
$$O\text{-}sec\text{-}C_4H_9 \qquad\qquad\qquad\qquad\qquad\qquad CH_3$$

$$XMg-O-C=CH-CH=CH-CH=CH-CH-R$$
$$\qquad\qquad | \qquad\qquad\qquad\qquad\qquad\qquad |$$
$$\qquad\qquad O\text{-}sec\text{-}C_4H_9 \qquad\qquad\qquad\qquad CH_3$$

$$(2)$$

although it should be borne in mind that the ester will probably first form a complex with one mole of Grignard reagent, the Grignard magnesium attacking the ester carbonyl oxygen. By this coordination the polarization within the conjugated system should be increased:

$$\begin{array}{c} R \\ \diagdown \\ Mg-O-C=CH-CH=CH-CH=CH-\overset{+}{C}H \\ \diagup \qquad | \qquad\qquad\qquad\qquad\qquad\qquad | \\ X \qquad O\text{-}sec\text{-}C_4H_9 \qquad\qquad\qquad\qquad CH_3 \end{array}$$

$$(3)$$

As previously discussed,[1] Michael additions to sorbic ester of active hydrogen compounds, such as malonic ester, probably proceed almost exclusively according to the carbanion mechanism *B* (2),** whereas conjugate additions

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* Similar views have recently been advanced by Miginiac.[11] The carbanion type of mechanism, here denoted *B*, appears to be favoured by Prévost.[12] See also the discussion at the end of this section (p. 2428).

** By the Michael addition, the presence of the terminal methyl group in sorbic and octatrienoic esters, as mentioned above, results in the formation of 1,4-adducts in considerable amounts, whereas β-vinylacrylic and heptatrienoic esters give exclusively 1,6- and 1,8-adducts, respectively.

of Grignard reagents take place preferentially by the cyclic mechanism, although the 1,6-addition, actually encountered also with Grignard reagents, indicates that this reaction also may follow the carbanion mechanism. This difference between the mechanism governing, on the one hand, the Michael addition reaction, and, on the other hand, the conjugate addition of Grignard reagents, appears quite reasonable in view of the essential ionic character of sodium derivatives *versus* the high degree of covalent character of the bond between magnesium and oxygen in the above complex compound (3) primarily formed from the ester and the Grignard reagent.

Although the mode of catalytic action of copper(I) chloride is still obscure, the available evidence renders it reasonable to believe that it exerts its effect by way of complex formation between the copper(I) ion and the carbon-carbon double bond. For the effects * on the course of the reactions between α,β-unsaturated esters and Grignard reagents we have tentatively suggested [15],[1] the primary formation of a copper(I) alkyl and the coordination of this with the ethylenic α-carbon atom of the unsaturated ester. The effect of such coordination could be two-fold: (i) a new cyclic, synchronous electron shift, A_{cu}, within a six-membered ring, involving a copper(I) alkyl attached to the α-carbon atom of the ester, might explain the 1,6-addition in the case of sorbic ester.[1] (ii) The coordination between the copper(I) ion and the α-carbon enhances the terminal polarization already present within the conjugated system and brought about by the carbonyl group; this effect should in any case favour conjugate addition to the terminal carbon atom of the conjugated system according to mechanism B (2).

Thus the following general mechanistic picture appears to emerge:

Conjugate addition of sodium derivatives of active hydrogen compounds (the Michael addition) always follows a carbanion mechanism (B), although the final products from these reversible processes are probably thermodynamically controlled.[8] The conjugate addition of Grignard reagents, on the other hand, is probably an irreversible process, and the mechanism may vary with the relative magnitudes of the energy of activation. The results so far appear to indicate that the product of the reaction is dependent on the unsaturated system in such a way, that conjugate addition takes place in satisfactory yield whenever the structure is such as to permit the formation of only one type of adduct as the result of the cooperation of more than one mechanism. In contrast, the low yields encountered may be explained by the non-cooperation of the various mechanisms, each of which favours its own type of conjugate addition; thus Michael additions and/or polymerization reactions meet little competition from any single conjugate addition reaction and therefore become fatal for conjugate addition in general.

With *crotonic* ester the terminal polarization effect favours the cyclic mechanism A (1) as well as the carbanion mechanism B (2), both leading to 1,4-addition. The presence of copper(I) chloride, increasing the terminal

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* These include the promotion of the hydrogenation of citraconic and mesaconic esters, [15] the change of orientation of the addition to acetylenic esters from 1,2- to 1,4-addition, [16] the above-mentioned change of orientation of the addition to sorbic ester from 1,4- to 1,6-addition,[1] as well as the general enhancement of conjugate addition.[17],[1]

polarization effect, is favourable to 1,4-addition. With *sorbic* ester the cyclic mechanism A (1) leads to 1,4-addition only, whereas the carbanion mechanism B (2) should give predominantly 1,6-addition, since the polarization is most strongly developed at the end of the conjugated system.[8] Thus none of the two conjugate addition reactions is particularly favoured, and the result is that other reactions (polymerization) take place to a large extent. Relatively low yields of simple conjugate addition products are obtained, preferentially the 1,4-adduct. In the presence of copper(I) chloride the terminal polarization effect, favouring 1,6-addition, is enhanced, and a new cyclic mechanism A_{cu}, likewise 1,6-directing, is made possible. The result is a high yield of almost exclusively 1,6-adduct. With *octatrienoic* ester the cyclic mechanism A (1) is 1,4-directing, while the carbanion mechanism B (2) is 1,8-directing. The polymerization which was already important in the case of sorbic ester, now becomes predominating, and practically no yield of conjugate addition products is obtained. In the presence of copper(I) chloride, the terminal polarization is strongly enhanced, and the carbanion mechanism B, leading to 1,8-addition, is consequently favoured. With octatrienoic, however, this terminal addition is not, as in the case of sorbic ester, further supported by a cyclic mechanism A_{cu} involving the copper(I) alkyl, since this mechanism would favour 1,6-addition only. Thus, the net result. is 1,8-addition, but only in low yield.

As was pointed out already by Alexander and Coraor,[18] it seems reasonable, therefore, to think of conjugate additions of Grignard reagents as being able to take place by more than one mechanism (*cf.* the foot-note on p. 2426). Although there is strong evidence that the cyclic electron shift within a six-membered ring represents a favourable transition state for the reaction, other mechanisms may be operative in cases where the former is hindered or precluded, or conditions are favourable for another mechanism. Probably some sort of carbanion mechanism is the one most likely among such other possibilities, and this mechanism may, furthermore, be specifically catalyzed by copper(I) chloride (*cf.* above). In this connection reference should be made to the cases of conjugate addition of methylmagnesium bromide to various cyclohex-2-enones reported in the literature. Here the cyclic mechanism is precluded, but nevertheless conjugate addition may take place, *e.g.* with cyclohex-2-en-1-one itself.[19],[18] In many cases, however, the reaction leads to 1,2-addition (to the carbonyl group) unless it is carried out in the presence of copper(I) chloride (or bromide), this catalyst drastically changing the orientation from 1,2- to 1,4-addition. Illustrative examples of this effect, discovered by Kharasch,[20] are the reactions of methylmagnesium bromide with isophorone,[20] with carvone and $\varDelta^{1(9)}$-octal-2-one,[21] and more recently with 6,6-ethylenedioxy-$\varDelta^{1(9)}$-octal-2-one.[22] Also 1,6-addition is encountered in cyclic systems when copper(I) chloride is present; thus, various $\varDelta^{4,6}$-3-oxo steroids react with methylmagnesium bromide to form the 7-methyl-$\varDelta^4$-3-oxo derivatives.[22a]

The fact that conjugate addition takes place also in cases where the cyclic mechanism is highly unlikely, led Alexander and Coraor [18] to consider this mechanism to be of minor importance. Recently, House and collaborators [23] interpret this and other stereochemical evidence as making "a cyclic process for conjugate addition appear most improbable". This, however, seems to be

a rather rigorous statement at the present moment. Firstly, one should be careful in making direct comparison between reactivities of cyclic and acyclic, unsaturated carbonyl compounds. The stereochemical conditions in the cyclic systems as well as the stereochemical consequences of the reactions seem not to be sufficiently elucidated as to justify categorical conclusions concerning the mechanism. House and Thomson [23] in their study of the stereochemistry of the conjugate addition admittedly discuss the structures and conformations of reactants and products, but also the thermodynamic effects of the possible creation or release of steric strain in the reactants deserve careful consideration, inasmuch as they may prove to be of fundamental significance for the reaction path and mechanism followed.* Secondly, there seems to be no reason why a mechanism, which is precluded in one particular case, should not be operative in another. On the other hand, our recent results, those reported in the present paper, as well as data obtained from further work in progress, lead also us to put less emphasis on the cyclic mechanism than we have done before. Still we think, however, that the results from the studies on sorbic ester,[1] *cis,trans*-isomeric unsaturated esters,[14] as well as the comparison of the reactivities towards crotonic ester of various butylmagnesium compounds [3] offer some support to the hypothesis that the cyclic transition state is of importance.

EXPERIMENTAL

Microanalyses were performed by Preben Hansen, Microanalytical Division, The Chemical Laboratory, The University of Copenhagen.

The fractional distillations were through a simple 45 cm × 8 mm Podbielniak-type column with a tantalum wire spiral, a heated jacket and a partial reflux head as described by Cason and Rapoport.[25] Boiling points are uncorrected. The infra-red spectrophometer and the gas-chromatograph ** were those previously used.[1]

Preparation of sec-*butyl octa-2,4,6-trienoate.* For the preparation of octa-2,4,6-trienoic acid several methods were tried,*** but none was found satisfactory. The procedure by which we obtained the best yields consisted in the synthesis of hexa-2,4-dienal (sorbaldehyde) by the zinc chloride catalyzed condensation between crotonaldehyde and vinyl ethyl ether according to Hoaglin, Kubler and Leech;[26] actually a mixture of sorbaldehyde and 3-ethoxyhex-4-enal was obtained, and this mixture was used in the subsequent Doebner condensation with malonic acid to form octatrienoic acid according to Kuhn and Hoffer.[27] In the preparation of sorbaldehyde and ethoxyhexenal [25] it was found essential that the crotonaldehyde was anhydrous.

To the commercial product (Fluka, pract.), containing about 10 % of water, solid sodium chloride was added, together with a small quantity of saturated sodium chloride solution. After standing overnight in the refrigerator the aqueous phase was separated, and the crotonaldehyde layer was distilled. As the water-crotonaldehyde azeotrop (containing 24 % of water) has the b.p. 84°, it could be separated by fractional distillation from pure crotonaldehyde, b.p. 103°. The forerun, b.p. up to 102° was subjected to repeated

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* In this connection attention should be drawn to the fact, pointed out by House and Thomson,[23] that no effect of copper (I) chloride on the stereoselectivity of the addition to cyclic a,β-unsaturated ketones was observed, whereas such an effect in the case of the non-cyclic system, a crotonic ester, has been reported by Inouye and Walborsky.[24]

** The gas-chromatographic work was performed (by Aa. J.) at Dansk Fedtforskningsinstitut, Copenhagen.

*** The valuable participation in this synthetic work by Torben Huld, Søren Rosendal Jensen, Carl Rydeng and Helge Jørgensen, students at the Polyteknisk Læreanstalt for the M. Sc. degree in chemical engineering, is gratefully acknowledged.

treatment with sodium chloride. The fraction, b.p. 102 — 103° was considered as dry croton-aldehyde. Only about a 40 % yield was obtained from the commercial product, but by repeated use of the foreruns the yield could be considerably increased. Also the recovered wet crotonaldehyde from the condensation with vinyl ethyl ether could be dried as de-scribed above and reused.
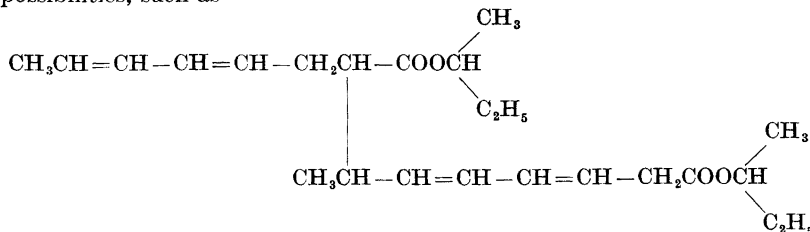
The total yield of octatrienoic acid varied between 6 and 12 % (calculated on the basis of vinyl ethyl ether).

The following other procedures for the preparation of octatrienoic acid gave negligible yields or failed completely, large quantities of polymerization products being formed in all cases: The Reformatsky addition of sec-butyl γ-bromocrotonate to crotonaldehyde to form 5-hydroxyocta-2,6-dienoic ester * which on elimination of water should give the desired ester,[28] the Wittig reaction between crotonaldehyde and the triphenylphospho-nium bromide from γ-bromocrotonic ester,[30] and the Doebner reaction between "König's salt" (from pyridine, monomethylaniline and cyanogen bromide) and malonic acid.[31]

From the acid the sec-butyl ester was obtained either by the standard esterification procedure for sec-butyl esters previously described [32],[33] or by the way of the crude acid chloride obtained by the use of thionyl chloride. By the former method the yield was 56 %, a large amount of polymerization products being formed, even if 1 % of hydro-quinone was added to the reaction mixture. This consisted of about 0.5 mole of the acid, 1 mole of butan-2-ol, 200 ml of benzene and 6 ml of concentrated sulfuric acid, the mixture being boiled under reflux for 5 h. The ester thus obtained had the b.p. 95 — 96°/0.8 mm, n_D^{25} 1.5481 (Found: C 74.20; H 9.29. Calc. for $C_{12}H_{18}O_2$ (194.26): C 74.19; H 9.34). The ester obtained from the acid chloride had the b.p. 84 — 86°/0.5 mm, n_D^{20} 1.5469, the yield being 73 %.

The addition reactions between butylmagnesium bromide and sec-butyl octatrienoate were carried out as previously described [32] or in the presence of copper(I) chloride, which was added in small portions concurrently with the addition of the ester to the Grignard reagent.[17] The addition were carried out in 0.1 mole runs, using 0.25 mole of Grignard reagent.

From the uncatalyzed reaction only traces, if any at all, of simple conjugation product could be isolated. However, a high-boiling product, b.p. 173 — 185°/0.5 mm, n_D^{20} 1.4920, was obtained in a yield corresponding to about 50 % of the octatrienoic ester used. The remaining residue decomposed on further heating. The minute amounts (0.6 g) of lower boiling products, which were obtained in one or two runs, contained, according to gas-cromatographic analysis, as the main component the 1,4-adduct; after hydrogena-tion: sec-butyl 3-butyloctanoate (I). The high-boiling compound might be some sort of a Michael addition product between one mole of octatrienoic ester and a molecule of ano-ther ester, either octatrienoic ester itself, a hydrogenation product thereof, or the con-jugate addition product.[34] The elemental analysis was most nearly correct for the second of these possibilities, such as

$$CH_3CH=CH-CH=CH-CH_2CH-COOCH \overset{CH_3}{\underset{C_2H_5}{<}}$$

$$CH_3CH-CH=CH-CH=CH-CH_2COOCH \overset{CH_3}{\underset{C_2H_5}{<}}$$

(Found: C 73.80; H 9.62. Calc. for the above compound, $C_{24}H_{38}O_4$ (390.54): C 73.80; H 9.81. For comparison, calc. for $C_{24}H_{36}O_4$ (388.53): C 74.19; H 9.34). Several attempts were made to vary the conditions for the uncatalyzed reaction so as to obtain higher yields of simple conjugate addition product, but no significant improvement was attained.
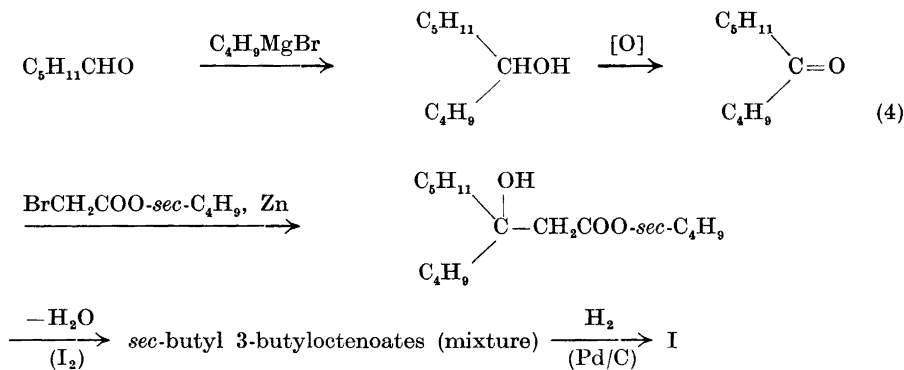
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* On the other hand, from recent results by Colonge and Varagnat [29] one might rather except this reaction to give predominantly the isomeric 2-vinyl-3-hydroxyhex-4-enoic ester.

In the copper(I) chloride catalyzed reactions the lower-boiling simple conjugate addition product was formed in $20-25$ % yields.* This product (5.1 g), b.p. $109-117°/0.9$ mm consisted, according to the gas-chromatographic analysis, of two components in about 2:1 ratio. A middle fraction of this product, b.p. $111-113°/0.7$ mm, n_D^{25} 1.4696, gave correct elemental analysis for a butyl-substituted octadienoic ester (Found: C 76.05; H 11.15. Calc. for $C_{16}H_{28}O_2$ (252.38): C 76.14; H 11.18). This product was hydrogenated catalytically to give one single compound, which was identified as *sec*-butyl 7-methylundecanoate (III).
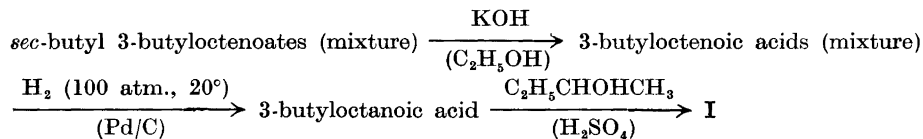
The unsaturated ester mixture (4.0 g) was dissolved in ethanol, 5 % Pd/BaSO$_4$ catalyst (5 g) was added, and the mixture was shaken for $1\frac{1}{4}$ h with hydrogen (2 atm.). After filtration and evaporation of the ethanol, the residue was distilled. The yield was 95 % (3.8 g), b.p. $106-117°/0.9$ mm, n_D^{25} 1.4343−1.4358, most of which (2.2 g) had the b.p. $113-115°/0.9$ mm, n_D^{25} 1.4343 (Found: C 74.80; H 12.51. Calc. for $C_{16}H_{32}O_2$ (256.42): C 74.94; H 12.58).

Preparation of authenic samples of the three tetra-hydro-adducts

sec-*Butyl 3-butyloctanoate* (I) was attempted prepared according to the following sequence of reactions:

$$C_5H_{11}CHO \xrightarrow{C_4H_9MgBr} \underset{C_4H_9}{\overset{C_5H_{11}}{\diagdown}}CHOH \xrightarrow{[O]} \underset{C_4H_9}{\overset{C_5H_{11}}{\diagdown}}C{=}O \qquad (4)$$

$$\xrightarrow{BrCH_2COO\text{-}sec\text{-}C_4H_9,\ Zn} \underset{C_4H_9}{\overset{C_5H_{11}}{\diagdown}}\overset{OH}{\underset{}{C}}-CH_2COO\text{-}sec\text{-}C_4H_9$$

$$\xrightarrow[\text{(I}_2\text{)}]{-H_2O} sec\text{-butyl 3-butyloctenoates (mixture)} \xrightarrow[\text{(Pd/C)}]{H_2} I$$

The last step of this reaction series, however, failed as no hydrogen was taken up even at 70° $(2-3$ atm.), and also an attempted hydrogenation by means of hydrogen iodide and red phosphorus [35] was unsuccessful. Instead the mixture of 3-butyloctenoic esters was saponified and the mixture of 3-butyloctenoic acids obtained was hydrogenated catalytically at 100 atm. at room temperature:

$$sec\text{-butyl 3-butyloctenoates (mixture)} \xrightarrow[\text{(C}_2\text{H}_5\text{OH)}]{KOH} \text{3-butyloctenoic acids (mixture)}$$

$$\xrightarrow[\text{(Pd/C)}]{H_2\ (100\ \text{atm., }20°)} \text{3-butyloctanoic acid} \xrightarrow[\text{(H}_2\text{SO}_4\text{)}]{C_2H_5CHOHCH_3} I$$

Decan-5-ol, b.p. $65-68°/0.9$ mm, n_D^{25} 1.4326 (rep. b.p. $118-120°/30$ mm, n_D^{27} 1.4321;[36] b.p. $117-118°/31$ mm, n_D^{25} 1.4310 [37]) was obtained in 46 % yield by the addition of the Grignard reagent from butyl bromide to hexanal (capronaldehyde, Fluka, *purum*), the procedure described in *Organic Syntheses* [38] for methyl isopropyl carbinol being used.

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* Also in this case attempts to improve the yield by varying the experimental conditions were unsuccessful.

Considerable amounts of a higher boiling product, b.p. $133-134°/1$ mm, n_D^{25} 1.4396, was obtained, presumably 2-butyl-3-hydroxyoctanal (capronaldol) (rep.[39] $138-141°/10$ mm), the yield being about 40 %. (Found: C 72.40; H 12.32. Calc. for $C_{12}H_{24}O_2$ (200.31): C 71.95; H 12.08).

Decan-5-one, b.p. $88-90°/13$ mm, n_D^{25} 1.4242 (rep. $106-108°/27$ mm, n_D^{24} 1.4225;[40] b.p. $84-86°/8$ mm, $n_D^{25.2}$ 1.4225;[36] b.p. $90°/13$ mm, n_D^{20} 1.4234 [41]) was obtained in at least 94 % yield by the oxidation of decan-5-ol, using sodium dichromate in sulfuric acid as described in *Organic Syntheses* [42] for the preparation of L-menthone.

sec-Butyl bromoacetate, b.p. $68-69°/11$ mm, n_D^{20} 1.4492, was obtained in 65 % yield essentially as described in *Organic Syntheses* [43] for the ethyl ester.

sec-Butyl 3-butyl octenoate (mixture ?). The Reformatsky reaction between decan-5-one (35.5 g, 0.23 mole) and *sec*-butyl bromoacetate (66.3 g, 0.34 mole) was carried out essentially as described by Cason [44,45] for the preparation of ethyl 3-methylnonenoate from octan-2-one. The crude 3-hydroxy-3-butyloctanoic ester (after removal of the solvent) was dehydrated by heating with iodine at 160° for 30 min. The total yield of 3-butyloctenoic ester (mixture ?), b.p. $90-114°/0.5$ mm, n_D^{20} $1.4455-1.4458$, was 75 % (43 g). The recovered ester from the below-mentioned unsuccessful hydrogenations was analyzed (Found: C 75.60; H 11.87. Calc. for $C_{16}H_{30}O_2$ (254.40): C 75.53; H 11.89).

sec-Butyl 3-butyloctanoate (I). Attempts were made to hydrogenate the above unsaturated ester mixture directly to the desired ester I by means of hydrogen at 2 atm. in the presence of palladium-on-carbon catalyst (10 % Pd/C). Even at 70° no reduction took place. The recovered unsaturated ester (35 g, 0.13 mole) was analyzed (see above) and then hydrolyzed by means of ethanolic potassium hydroxide to a mixture of the free 3-butyloctenoic acids, b.p. $112-120°/0.5$ mm, n_D^{20} $1.4566-1.4586$, the yield being 92 % (25.3 g). (Neutr. equiv. found: 195. Calc. for $C_{12}H_{22}O_2$: 198). This acid mixture (25 g, 0.13 mole), dissolved in ethanol, was shaken for 2 h at room temperature with hydrogen at 100 atm in the presence of 10 % palladium-on-carbon (2 g), yielding 84 % (21.4 g) of 3-butyloctanoic acid, b.p. $100-112°/0.5$ mm, n_D^{20} $1.4422-1.4426$; the major part, 75 % (19.5 g), had the b.p. $107-108°/0.5$ mm, n_D^{20} 1.4425. (Found: C 71.65; H 11.88. Calc. for $C_{12}H_{24}O_2$ (200.31): C 71.95; H 12.08).

The 3-butyloctanoic acid (10 g) was esterified with butan-2-ol (20 g) according to the usual esterification procedure previously described,[33] giving almost quantitative yield (13.5 g, 95 %) of *sec*-butyl 3-butyloctanoate (I), b.p. $89-94°/0.5$ mm. An analytical sample, shown by gas chromatography to be pure, had the b.p. $89°/0.5$ mm, n_D^{20} 1.4346 (Found: C 74.80; H 12.40. Calc. for $C_{16}H_{32}O_2$ (256.42): C 74.94; H 12.58).

sec-Butyl 5-propylnonanoate (II) was obtained according to the following scheme:

$$\text{(5)}$$
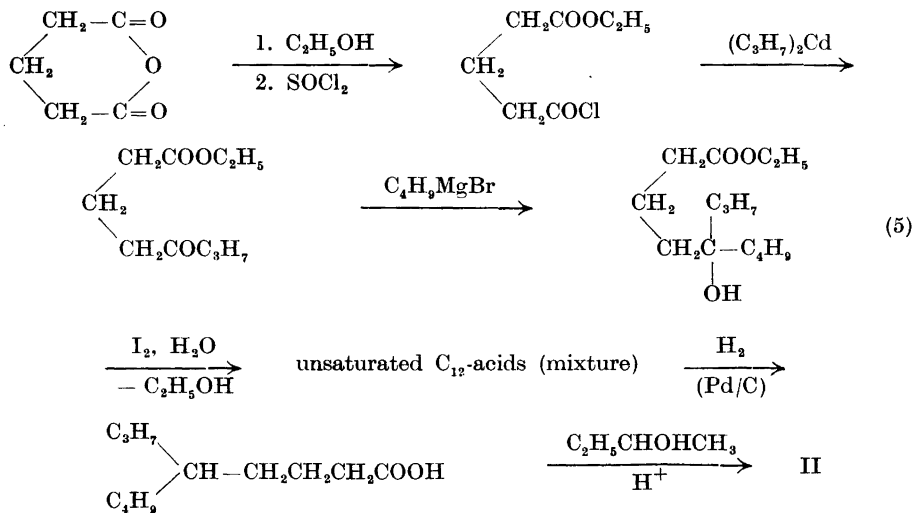
Monoethyl glutarate (γ-ethoxycarbonyl-butyric acid), b.p. $158-162°/15$ mm, (rep.[46] $159-165°/17$ mm) was obtained in 88 % yield as described by Bachmann [46] by heating a solution of glutaric anhydride (Fluka, *purum*) in absolute ethanol for 2 h under reflux.

γ-Ethoxycarbonyl-butyryl chloride was obtained essentially as described by Cason [47] for β-ethoxycarbonyl-propionyl chloride: The above monoester (124 g, 0.77 mole) and thionyl chloride (122 g, 75 ml, 1.4 mole) was heated to 40° and left at room temperature for 3 days and distilled. The yield of product, b.p. $105-110°/12$ mm, rep.[46] $108-110°/15$ mm) was 93 % (126 g) and 80 % calculated on the basis of glutaric anhydride.
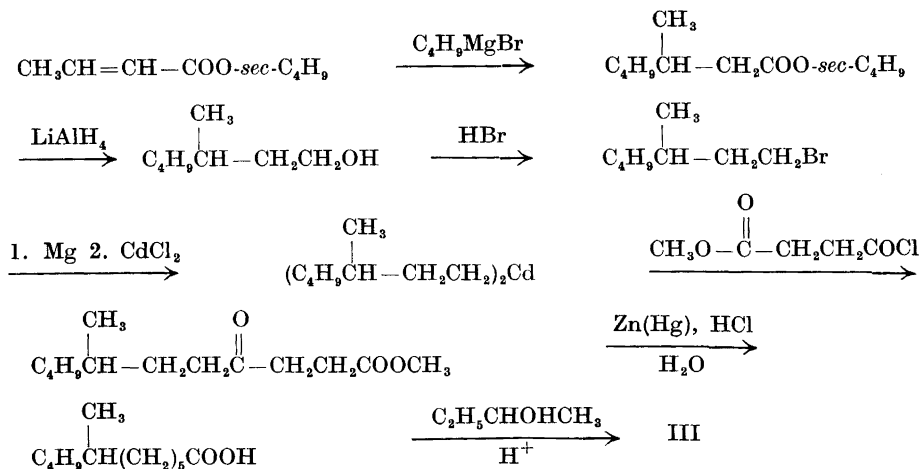
Ethyl 5-oxoöctanoate (eqn. 5) was synthesized employing the cadmium reaction as described by Cason [48],[49] from dipropylcadmium (1 mole) and γ-ethoxycarbonyl-butyryl chloride (126 g, 0.70 mole). There was obtained 93 g (72 %) of ester in three fractions of equal size (about 30 g), b.p. $78-80°/0.7-0.8$ mm, n_D^{25} $1.4280-1.4293$. The second fraction, b.p. $79°/0.8$ mm, n_D^{25} 1.4384, was analyzed but was found not to be pure. (Found: C 62.35; H 9.48. Calc. for $C_{10}H_{18}O_3$ (186.24): C 64.49; H 9.74). The b.p. $115-118°/10$ mm has been reported.[50]

5-Propylnonanoic acid was attempted prepared *via* its ethyl ester according to the procedure of Cason [51] for the synthesis of ethyl 6-methyloctanoate. To the above ethyl 5-oxoöctanoate (93 g, 0.5 mole), dissolved in ether (400 ml), the Grignard reagent (0.6 mole) from butyl bromide was added dropwise (by syphoning) during 3 ½ h, with stirring and cooling in ice-bath. After another hour of stirring and cooling the mixture was hydrolyzed, separated and extracted with ether. After removal of the solvent a few crystals of iodine were added to the residue, which was then heated to $180-200°$ for 30 min. The crude product, b.p. $86-133°/0.9$ mm, was subject to attempted hydrogenation at room temperature, employing hydrogen of 2 atm. and a 5 % palladium-on-carbon catalyst, but no hydrogen uptake was detected. The product, after purification was redistilled (46.1 g), b.p. $113-128°/1$ mm; its infra-red spectrum indicated the presence of a free carboxyl group, the elemental analysis pointed to an unsaturated acid, and the neutral equivalent was determined to be 208 (calc. for 5-propylnonenoic acid: 198). The reaction with bromine, however, resulted in the evolution of hydrogen bromide, indicating a substitution taking place. After another attempted but unsuccessful catalytic hydrogenation, this time at 50 atm., the distilled product (41.5 g) was dissolved in ether, and the solution extracted with 2 N sodium hydroxide.* From the aqueous extract, after acidification and extraction, there was obtained in total 15 g of product, b.p. $107-111°/0.5$ mm, n_D^{20} $1.4576-1.4583$. Of this 12.4 g had the b.p. $109-110°/0.5$ mm, n_D^{20} 1.4583, and gave the correct analytical data for an unsaturated C_{12}-acid mixture (Found: C 72.75; H 11.08. Calc. for $C_{12}H_{22}O_2$ (198.30): C 72.68; H 11.18). This product (15 g) was dissolved in ethanol (100 ml), mixed with 10 % palladium-on-carbon (2 g) and shaken for 2 h with hydrogen of 100 atm. There was obtained in total 12 g, b.p. $105-110°/0.5$ mm, n_D^{20} $1.4452-1.4447$. The fraction (6 g), b.p. $108-110°/0.5$ mm, n_D^{20} 1.4447, showed the correct analysis for 5-propylnonanoic acid (Found: C 71.85; H 11.91. Calc. for $C_{12}H_{24}O_2$ (200.31): C 71.95; H 12.08).

sec-*Butyl 5-propylnonanoate* (II). The above 5-propylnonanoic acid (10 g) was esterified with butan-2-ol (20 g) as previously described.[33] The yield of the desired ester II, b.p. $96-97°/0.6$ mm, n_D^{20} 1.4360, was 96 % (12.3 g). (Found: C 74.85; H 12.44. Calc. for $C_{16}H_{32}O_2$ (256.42): C 74.94; H 12.58).

sec-*Butyl 7-methylundecanoate* (III). The corresponding acid was obtained by the Clemmensen reduction of the γ-ketoester produced from the reaction between the 3-methylheptylcadmium reagent and β-methoxycarbonyl-propionyl chloride. The reactions employed were the following:

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* The ether-soluble neutral product (25 g) showed the b.p. $78-105°$ 0.5 mm, n_D^{20} $1.4469-1.4558$. It was, for the time being, not further investigated.

$$CH_3CH=CH-COO\text{-}sec\text{-}C_4H_9 \xrightarrow{C_4H_9MgBr} \overset{\overset{\displaystyle CH_3}{|}}{C_4H_9CH}-CH_2COO\text{-}sec\text{-}C_4H_9$$

$$\xrightarrow{LiAlH_4} \overset{\overset{\displaystyle CH_3}{|}}{C_4H_9CH}-CH_2CH_2OH \xrightarrow{HBr} \overset{\overset{\displaystyle CH_3}{|}}{C_4H_9CH}-CH_2CH_2Br$$

$$\xrightarrow{1.\ Mg\ 2.\ CdCl_2} \left(\overset{\overset{\displaystyle CH_3}{|}}{C_4H_9CH}-CH_2CH_2\right)_2Cd \qquad CH_3O-\overset{\overset{\displaystyle O}{||}}{C}-CH_2CH_2COCl \longrightarrow$$

$$\overset{\overset{\displaystyle CH_3}{|}}{C_4H_9CH}-CH_2CH_2\overset{\overset{\displaystyle O}{||}}{C}-CH_2CH_2COOCH_3 \xrightarrow[H_2O]{Zn(Hg),\ HCl}$$

$$\overset{\overset{\displaystyle CH_3}{|}}{C_4H_9CH}(CH_2)_5COOH \xrightarrow[H^+]{C_2H_5CHOHCH_3} III$$

sec-*Butyl 3-methylheptanoate*, b.p. 115°/25 mm, n_D^{25} 1.4198 (rep.[33] 92—93°/9 mm, n_D^{25} 1.4190) was obtained as previously described.[33] β-*Methoxycarbonyl-propionyl chloride* was prepared by the method of Cason[47].

3-*Methylheptan-1-ol*.[52] To lithium aluminium hydride (15.4 g, 0.41 mole) in dry ether (600 ml) was added with stirring a solution of sec-butyl 3-methylheptanoate (130 g, 0.65 mole) in ether (150 ml) at such a rate as to secure gentle reflux (about 1 h). Stirring was continued at room temperature for another hour. Then water was added dropwise in order to destroy the excess of lithium aluminium hydride. The reaction mixture was poured into hydrochloric acid, and the etheral layer was washed with water and sodium bicarbonate. There was obtained an 84 % yield (70.8 g) of product, b.p. 83—90°/14 mm, n_D^{25} 1.4263—1.4281. The major part (60.3 g) had the b.p. 86—87°/14 mm, n_D^{25} 1.4278 (rep. b.p. 101°/26 mm, n_D^{23} 1.4293;[53] b.p. 87.7°/20 mm, n_D^{25} 1.4225[54]; b.p. 80°/20 mm, n_D^{20} 1.4285[55]). (Found: C 73.60; H 13.97. Calc. for $C_8H_{18}O$ (130.22): C 73.78; H 13.92).

1-*Bromo-3-methylheptane* was prepared by boiling the above alcohol (70.8 g, 0.68 mole) with hydrobromic acid as described in *Organic Syntheses*[56] for octyl bromide. The yield of product, b.p. 73—74°/12 mm, n_D^{20} 1.4538, was 57 % (74.2 g). It was probably contaminated with a small amount of the alcohol, as indicated by gas chromatography and the analysis (Found: C 50.25; H 9.25. Calc. for $C_8H_{17}Br$ (193.14): C 49.75; H 8.87).

Methyl 4-oxo-7-methylundecanoate. This γ-ketoester was prepared from 1-bromo-3-methylheptane (71.2 g, 0.37 mole) and β-methoxycarbonyl-propionyl chloride (55.5 g, 0.37 mole), employing the cadmium reaction as described by Cason[48,49] for the preparation of methyl 4-oxo-7-methyloctanoate. The yield of product, b.p. 110—114°/0.9 mm, n_D^{20} 1.4436, was 38 % (32.5 g). (Found: C 68.25; H 10.46. Calc. for $C_{13}H_{24}O_3$ (228.32): C 68.38; H 10.59).

7-*Methylundecanoic acid* was obtained by the Clemmensen reduction of the above keto ester (32.5 g, 0.14 mole). The procedure followed was that used by Cason[57] for the preparation of 7-methyloctanoic acid. The yield of fatty acid, b.p. 124°/0.9 mm, n_D^{20} 1.4457, was 78 % (22 g). (Found: C 72.10; H 11.91. Calc. for $C_{12}H_{24}O_2$ (200.31): C 71.95; H 12.08).

sec-*Butyl 7-methylundecanoate* (III). The above 7-methylundecanoic acid (10 g) was esterified with butan-2-ol (20 g) as previously described.[33] The yield of the desired ester III, b.p. 120—122°/1.5 mm, n_D^{25} 1.4348, was 55 % (7 g). (Found: C 75.10; H 12.64. Calc. for $C_{16}H_{32}O_2$ (256.42): C 74.94; H 12.58).

The three esters I, II and III were found by gas chromatography to be pure. They were easily separable on a 2 m silicone (Elastomer E 301 on Celite) column showing retention times increasing in the order given.

REFERENCES

1. Munch-Petersen, J., Bretting, C., Møller Jørgensen, P., Refn, S., Andersen, V. K. and Jart, Aa. *Acta Chem. Scand.* **15** (1961) 277.
2. Kohler, E. P. and Butler, F. R. *J. Am. Chem. Soc.* **48** (1926) 1036; for further references, see Ref.[1]
3. Munch-Petersen, J. and Jacobsen, S. *Compt. Rend.* **255** (1962) 1355; Jacobsen, S., Bitsch, V. and Munch-Petersen, J. *Acta Chem. Scand.* **17** (1963) 825.
4. Bertrand, M. and Le Gras, J. *Bull. Soc. Chim. France* **1962** 2136; *cf.* also Ref.[23]
5. Farmer, E. H. and Martin, S. R. W. *J. Chem. Soc.* **1933** 960.
6. Acker, D. S. and Anderson, B. C. *J. Org. Chem.* **24** (1959) 1162.
7. Farmer, E. H. and Healy, A. T. *J. Chem. Soc.* **1927** 1060; Farmer, E. H. and Metha, T. N. *J. Chem. Soc.* **1930** 1610; **1931** 1904; Bloom, J. and Ingold, C. K. *J. Chem. Soc.* **1931** 2765; *cf.* Ref.[1]
8. Ingold, C. K. *Structure and Mechanism in Organic Chemistry*, Cornell University Press, Ithaca, N. Y. 1953, pp. 697–699.
9. Fuson, R. C. and Mange, F. E. *J. Org. Chem.* **19** (1954) 806.
10. Chapman, O. L., Pasto, D. J. and Griswold, A. A. *J. Am. Chem. Soc.* **84** (1962) 1213.
11. Miginiac, P. *Ann. Chim.* **7** (1962) 471 ff.
12. Andrac, M., Gaudemar, F., Gaudemar, M., Gross, B., Miginiac, L., Miginiac, P. and Prévost, C. *Bull. Soc. Chim. France* **1963** 1385.
13. Lutz, R. E. and Reveley, W. G. *J. Am. Chem. Soc.* **63** (1941) 3180.
14. Kindt-Larsen, T., Bitsch, V., Krogh Andersen, I. G., Jart, Aa. and Munch-Petersen, J. *Acta Chem. Scand.* **17** (1963) 1426.
15. Bjerl Nielsen, E., Munch-Petersen, J., Møller Jørgensen, P. and Refn, S. *Acta Chem. Scand.* **13** (1959) 1943.[1]
16. Bretting, C., Munch-Petersen, J., Møller Jørgensen, P. and Refn, S. *Acta Chem. Scand.* **14** (1960) 151.
17. Munch-Petersen, J. and Andersen, V. K., *Acta Chem. Scand.* **15** (1961) 271.
18. Alexander, E. R. and Coraor, G. R. *J. Am. Chem. Soc.* **73** (1951) 2721.
19. Whitmore, F. C. and Pedlow, G. W. *J. Am. Chem. Soc.* **63** (1941) 758.
20. Kharasch, M. S. and Tawney, P. O. *J. Am. Chem. Soc.* **63** (1941) 2308.
21. Birch, A. J. and Robinson, R. *J. Chem. Soc.* **1943** 501; *cf.* Birch, A. J. and Smith, M. *Proc. Chem. Soc.* **1962** 356.
22. Church, R. F., Ireland, R. E. and Shridhar, D. R. *J. Org. Chem.* **27** (1962) 707.
22a. Campbell, J. A. and Babcock, J. C. *J. Am. Chem. Soc.* **81** (1959) 4069; Atwater, N. W., Bible, R. H., Brown, E. A., Burntner, R. R., Mihina, J. S., Nysted, L. N. and Sollman, P. B. *J. Org. Chem.* **26** (1961) 3077.
23. House, H. O. and Thompson, H. W. *J. Org. Chem.* **28** (1963) 360; *cf.* also House, H. O., Traficante, D. D. and Evans, R. A. *J. Org. Chem.* **28** (1963) 348; House, H. O. and Traficante, D. D. *J. Org. Chem.* **28** (1963) 355.
24. Inouye, Y. and Walborsky, H. M. *J. Org. Chem.* **27** (1962) 2706.
25. Cason, J. and Rapoport, H. *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., Englewood Cliffs, N. J., 2nd. Ed. 1962, p. 289 ff.
26. Hoaglin, R. I., Kubler, D. R. and Leech, R. F. *J. Am. Chem. Soc.* **80** (1958) 3069.
27. Kuhn, R. and Hoffer, M. *Ber.* **63** (1930) 2164.
28. Jones, E. R. H., O'Sullivan, D. G. and Whiting, M. C. *J. Chem. Soc.* **1949** 1418.
29. Colonge, J. and Varagnat, J. *Bull. Soc. Chim. France* **1961** 234; **1963** 1453.
30. Bohlmann, F. *Chem. Ber.* **90** (1957) 1519; *cf.* Isler, O., Gutmann, H., Montavon, M., Rüegg, R., Ryser, G. and Zeller, P. *Helv. Chim. Acta* **40** (1957) 1257; Kucherov, V. F., Kovalev, B. G., Nazarova, I. I. and Yanovskaya, L. A. *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk* **1960** 1512 (English translation by Consultants Bureau, p. 1405).
31. Grewe, R. and v. Bonin, W. *Chem. Ber.* **94** (1961) 234.
32. Munch-Petersen, J. *J. Org. Chem.* **22** (1957) 170.
33. Munch-Petersen, J. *Org. Syn.* **41** (1961) 60.

34. *Cf.* Bitsch, V., Jacobsen, S., Krogh Andersen, I. G. and Munch-Petersen, J. *Acta Chem. Scand.* **17** (1963) 1433.
35. Miescher, K. and Billeter, J. R. *Helv. Chim. Acta* **22** (1939) 601.
36. Woods, G. F. and Lederle, H. F. *J. Am. Chem. Soc.* **73** (1951) 2245.
37. Zeiss, H. H. and Tsutsui, M. *J. Am. Chem. Soc.* **75** (1953) 897.
38. Drake, N. L. and Cooke, G. B. *Org. Syn.* Coll. Vol. **II** (1943) 406.
39. Astle, M. J. and Zaslowsky, J. A. *Ind. Eng. Chem.* **44** (1952) 2867.
40. Bried, E. A. and Hennion, G. F. *J. Am. Chem. Soc.* **60** (1938) 1717.
41. Franzen, V. *Chem. Ber.* **87** (1954) 1478.
42. Sandborn, L. T. *Org. Syn.* Coll. Vol. **I**, 2nd. Ed. (1941) 340.
43. Natelson, S. and Gottfried, S. *Org. Synt.* Coll. Vol. **III** (1955) 382.
44. Ref.[25], p. 470.
45. *Cf.* Rinehart, K. L. and Perkins, E. G. *Org. Syn.* **37** (1957) 37.
46. Bachmann, W. E., Kushner, S. and Stevenson, A. C. *J. Am. Chem. Soc.* **64** (1942) 974.
47. Cason, J. *Org. Syn.* Coll. Vol. **III** (1955) 169.
48. Cason, J. and Prout, F. S. *Org. Syn.* Coll. Vol. **III** (1955) 601.
49. Ref.[25], p. 456 ff.; 466 ff.
50. Nakazawa, K. and Matsuura, S. *J. Pharm. Soc. Japan* **71** (1951) 802; [*Chem. Abstr.* **46** (1952) 8025 f].
51. Cason, J. *J. Am. Chem. Soc.* **66** (1944) 46.
52. *Cf.* Brown, W. G. *Org. Reactions* **6** (1951) 469 ff.
53. Huston, R. C. and Agett, A. H. *J. Org. Chem.* **6** (1941) 123.
54. Dorough, G. L., Glass, H. B., Gresham, T. L., Malone, G. B. and Reid, E. E. *J. Am Chem. Soc.* **63** (1941) 3100.
55. Lichtenberger, J. and Dürr, L. *Bull. Soc. Chim. France* **1956** 664.
56. Kamm, O. and Marvel, C. S. *Org. Syn.* Coll. Vol. **I**, 2nd. Ed. (1941) 30.
57. Cason, J. *J. Am. Chem. Soc.* **64** (1942) 1106.