89. *Addition of βγ-Unsaturated Alcohols to the Active Methylene Group. Part III. Scope and Mechanism of the Reaction.*

By M. F. Carroll.

A study of the action of various alcohols on compounds containing an active methylene group at 150—250° in the presence of an alkaline catalyst has shown that only βγ-unsaturated alcohols give normal addition products. An apparently similar reaction occurs with some βγ-unsaturated alcohols and certain aromatic alcohols. The mechanism of these reactions is discussed, and the results applied to explain some analogous reactions.

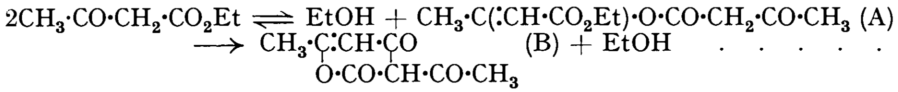
The reactivity of groups attached to the active methylene group is in the order: $CH_2(CO_2R)_2 > R{\cdot}CO{\cdot}CH_2{\cdot}CO_2R' > R{\cdot}CO{\cdot}CHR'{\cdot}CO_2R'' > R{\cdot}CO{\cdot}CH_2{\cdot}COR'$.

Ethyl acetoacetate and βγ-unsaturated alcohols give unsaturated ketones as final products of the reaction (J., 1940, 704, 1266). The work already reported was part of a more extensive study of the reaction between alcohols and compounds containing an active methylene group. It is now shown that only βγ-unsaturated alcohols give addition products, but the results for other alcohols are given, as these show the effect of the carbinol group alone.

The procedure consists in heating the reactants in presence of sodium acetate. Other alkaline catalysts, *e.g.*, sodium ethoxide, potassium hydroxide, have the same effect. The mechanism of the reaction is more complicated than was thought, and the products obtained from ethyl acetoacetate and an alcohol ROH were EtOH, CO_2, $CH_3{\cdot}CO_2R$, $CH_3{\cdot}CO{\cdot}CH_3$, $CH_3{\cdot}CO{\cdot}CH_2R$ (or R′ where rearrangement occurs), and the olefin from ROH. Ethyl malonate and βγ-unsaturated alcohols give the unsaturated acid R(or R′)$\cdot CH_2{\cdot}CO_2H$. The Table shows the mol. % of ester, ketone, olefin, and acid.

Exp.		Ester.	Ketone.	Olefin.
	(1) *Ethyl Acetoacetate and Saturated Alcohols.*			
1	Ethyl alcohol	2	0	0
2	Butyl alcohol	4	0	0
3	Heptyl alcohol	14	0	0
4	Benzyl alcohol	46	<1	0
5	Phenylethyl alcohol	42	0	3
6	Anisyl alcohol	55	0	0
7	Phenylmethylcarbinol	11	<1	11
8	Phenylmethylethylcarbinol	0	0	83
	(2) *Ethyl Acetoacetate and Unsaturated Alcohols.*			
9	Allyl alcohol	6	<1	0
10	Methallyl alcohol	9	<2	0
11	Crotyl alcohol	21	8	0
12	Methylvinylcarbinol	12	12	0
13	Geraniol	16	12	trace
14	Linalool	10	41	,,
15	Cinnamyl alcohol	16	33	0
16	Phenylvinylcarbinol	5	75	0
17	*iso*Pulegol	12	<2	5
	(3) *Ethyl Butylacetoacetate and Unsaturated Alcohols.*			
18	Methallyl alcohol	49	<1	0
19	Cinnamyl alcohol	40	15	0
20	Linalool	10	27	trace
	(4) *Ethyl Malonate and Unsaturated Alcohols.*			
21	Allyl alcohol	6% unsaturated acid		
22	Crotyl alcohol	13% ,, ,,		
23	Cinnamyl alcohol	66% ,, ,,		
24	Phenylvinylcarbinol	51% ,, ,,		

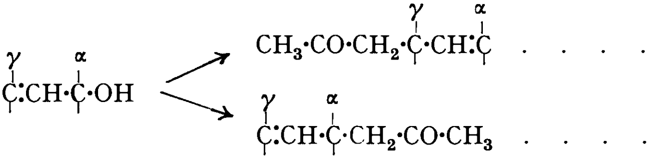
The results given in section (1) of the Table may be regarded as an extension of the work of Arndt and co-workers (*Ber.*, 1936, **69**, 2373), who investigated the formation of dehydroacetic acid from ethyl acetoacetate. Arndt represents the course of this reaction as follows :



$$\begin{array}{l} 2CH_3\cdot CO\cdot CH_2\cdot CO_2Et \rightleftharpoons EtOH + CH_3\cdot C(:CH\cdot CO_2Et)\cdot O\cdot CO\cdot CH_2\cdot CO\cdot CH_3 \text{ (A)} \\ \qquad \longrightarrow \begin{array}{l} CH_3\cdot C:CH\cdot CO \\ \quad | \qquad\quad | \\ \quad O\cdot CO\cdot CH\cdot CO\cdot CH_3 \end{array} \text{ (B)} + EtOH \quad . \; . \; . \; . \; . \quad (1) \end{array}$$

With alcohols which readily undergo alcoholysis the ethyl group of (A) is replaced by the R of the alcohol ROH, and ethyl alcohol distils quantitatively. At a higher temperature decomposition ensues with the formation of the products tabulated above. If ROH is volatile, R is removed as the alcohol, leaving dehydracetic acid or its decomposition products, but if ROH is sufficiently high-boiling, it remains in equilibrium with (A) and becomes acetylated. This explains the low ester number for heptyl alcohol, as this alcohol (b. p. 177°) distils slowly during the reaction. High-boiling alcohols such as benzyl and phenylethyl alcohol give the maximum amount of ester, and the figure (50% approx.) suggests that the acetyl group of (A) or (B) is the effective acetylating agent. Acetone is produced in every case, particularly at the higher temperature, and is probably formed from (A).

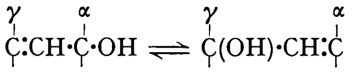
Section (2) of the Table shows that the lower βγ-unsaturated alcohols behave in regard to ester and ketone formation in the same way as the lower saturated alcohols do in regard to ester formation. Exp. 17 shows that the addition does not take place with γδ-unsaturated alcohols. The effect of βγ-unsaturation is seen from a comparison of butyl and crotyl alcohols, the b. p.'s of which are nearly the same. The effect of substituents is shown by two alcohols of the same b. p. : methylvinylcarbinol with an α-substituent gives more ketone than methallyl alcohol with a β-substituent.



$$\overset{\gamma}{\underset{|}{\overset{|}{C}}}:CH\cdot\overset{\alpha}{\underset{|}{\overset{|}{C}}}\cdot OH \begin{array}{l} \nearrow CH_3\cdot CO\cdot CH_2\cdot\overset{\gamma}{\underset{|}{\overset{|}{C}}}\cdot CH:\overset{\alpha}{\underset{|}{\overset{|}{C}}} \quad . \; . \; . \; . \; . \quad (2a) \\ \searrow \overset{\gamma}{\underset{|}{\overset{|}{C}}}:CH\cdot\overset{\alpha}{\underset{|}{\overset{|}{C}}}\cdot CH_2\cdot CO\cdot CH_3 \quad . \; . \; . \; . \; . \quad (2b) \end{array}$$

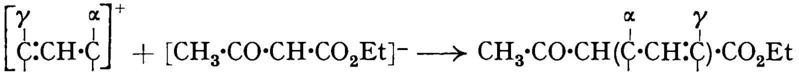
Addition to the active methylene group may take place in two ways, the normal or γ-addition and the "transposed" or α-addition (2*b*). The reaction (2*a*) proceeds more readily than (2*b*), which gives less ketone but more ester. The alcohols in section (2) give only a single addition product, with the possible exception of linalool, but exps. 23 and 24 provide some evidence of α- and γ-addition in each case.

The occurrence of α-addition introduces complications in the mechanism of the reaction. The experimental conditions do not favour anionotropic change (cf. Burton and



$$\overset{\gamma}{\underset{|}{\overset{|}{C}}}:CH\cdot\overset{\alpha}{\underset{|}{\overset{|}{C}}}\cdot OH \rightleftharpoons \overset{\gamma}{\underset{|}{\overset{|}{C}}}(OH)\cdot CH:\overset{\alpha}{\underset{|}{\overset{|}{C}}} \quad . \; . \; . \; . \; . \; . \; . \quad (3)$$

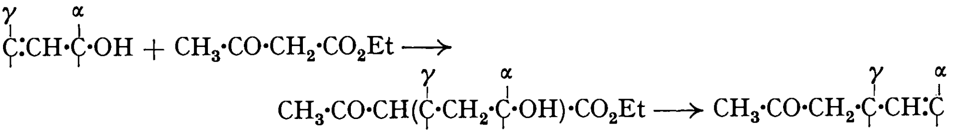
Ingold, J., 1928, 906) and linalool and geraniol show no interconversion under similar conditions. The α-addition may be represented



$$\left[\overset{\gamma}{\underset{|}{\overset{|}{C}}}:CH\cdot\overset{\alpha}{\underset{|}{\overset{|}{C}}}\right]^+ + [CH_3\cdot CO\cdot CH\cdot CO_2Et]^- \longrightarrow CH_3\cdot CO\cdot CH(\overset{\alpha}{\underset{|}{\overset{|}{C}}}\cdot CH:\overset{\gamma}{\underset{|}{\overset{|}{C}}})\cdot CO_2Et \quad . \quad (4)$$

but it is necessary to postulate an α ⟶ γ shift to account for the γ-addition. This mechanism fails to explain the behaviour of the linalool–geraniol pair, as the γ-addition product is formed at a much lower temperature than the α. Also, the shift should yield mixtures of α- and γ-addition products in all cases, but it was shown (*loc. cit.*) that the cinnamyl alcohol–phenylvinylcarbinol pair each gave only one compound, the corresponding γ-addition product.

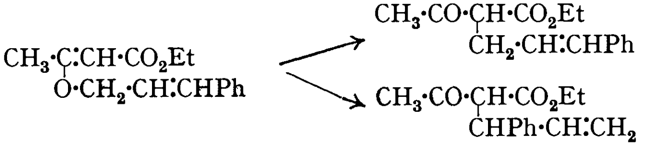
Two different mechanisms are therefore involved, γ-addition taking place before removal of the hydroxyl group,



$$\overset{\gamma}{\text{C}}\text{:CH·}\overset{\alpha}{\text{C}}\text{·OH} + \text{CH}_3\text{·CO·CH}_2\text{·CO}_2\text{Et} \longrightarrow \text{CH}_3\text{·CO·CH(}\overset{\gamma}{\text{C}}\text{·CH}_2\text{·}\overset{\alpha}{\text{C}}\text{·OH)·CO}_2\text{Et} \longrightarrow \text{CH}_3\text{·CO·CH}_2\text{·}\overset{\gamma}{\text{C}}\text{·CH:}\overset{\alpha}{\text{C}} \quad (5)$$

whereas α-addition takes place according to (4).

A similar explanation may be given of the results of Bergmann and Corte (J., 1935, 1363), who rearranged ethyl β-cinnamyloxycrotonate by heating to 260° and obtained mainly the α-addition product, together with some of the normal product.



$$\begin{array}{l}\text{CH}_3\text{·}\underset{|}{\text{C}}\text{:CH·CO}_2\text{Et}\\ \quad\text{O·CH}_2\text{·CH:CHPh}\end{array} \begin{array}{l} \nearrow \begin{array}{l}\text{CH}_3\text{·CO·}\underset{|}{\text{C}}\text{H·CO}_2\text{Et}\\ \qquad\text{CH}_2\text{·CH:CHPh}\end{array} \quad . \; . \; . \quad (6a) \\ \searrow \begin{array}{l}\text{CH}_3\text{·CO·}\underset{|}{\text{C}}\text{H·CO}_2\text{Et}\\ \qquad\text{CHPh·CH:CH}_2\end{array} \quad . \; . \; . \quad (6b)\end{array}$$

Using ammonium chloride at 140°, Lauer and Kilburn (*J. Amer. Chem. Soc.*, 1937, **59**, 2856) found only the normal compound (6*b*). The former authors regard (6*a*) as the normal product, but in the analogous rearrangement of the phenyl allyl ethers the normal reaction corresponds to (6*b*). Although in the latter reaction an abnormal rearrangement with addition at the β-carbon atom has been observed by Lauer *et al.* (*J. Amer. Chem. Soc.*, 1936, **58**, 1388 *et seq.*), compounds corresponding to equation (4) are not formed, and they are only produced in other reactions by a simple ionic mechanism, *e.g.*, by the action of cinnamyl halides on phenols in the presence of alkali and non-polar solvents.

Benzyl alcohol may be regarded as a $\beta\gamma$-unsaturated alcohol, the γ-carbon corresponding to the *o*-position; *e.g.*, benzylmagnesium chloride and formaldehyde give *o*-tolylcarbinol (Tiffeneau and Delange, *Compt. rend.*, 1903, **137**, 537; Gilmour and Breuer, *J. Amer. Chem. Soc.*, 1934, **56**, 1127). But none of the aromatic alcohols in section (1) of the Table gave addition products with ethyl acetoacetate. In this connection it may be noted that phenyl benzyl ethers do not give the phenyl allyl ether rearrangement (Hurd, " Pyrolysis of Carbon Compounds," p. 222). Fosse (*Compt. rend.*, 1907, **145**, 196, 1292) has shown, however, that some di- and tri-phenylcarbinols react with the active methylene group, but this reaction is similar to (4) and no mention is made of *o*-substitution products. Some of this work was repeated with and without catalysts, but no *o*-substitution was observed. Triphenylcarbinol and ethyl malonate gave $\beta\beta\beta$-triphenylpropionic acid as the only acidic product, and with ethyl acetoacetate only triphenylmethane could be isolated. Benzyl alcohol and butyl malonate, on prolonged refluxing, gave a small quantity of the α-addition product, β-phenylpropionic acid. Hence it may be concluded that γ-addition occurs only when certain groups are present on the α- or γ-carbon atom of $\beta\gamma$-unsaturated alcohols, and α-addition is due to activation by the $\beta\gamma$-double bond or by β-aromatic substituents.

Ethyl butylacetoacetate with the alcohol ROH gives EtOH, CO_2, $CH_3{\cdot}CO{\cdot}CH_2Bu$, $CH_3{\cdot}CO_2R$, $CH_3{\cdot}CO{\cdot}CHBuR$ (or R′), and $CH_2Bu{\cdot}CO_2Et$. The constitution of the unsaturated ketone was not determined. In exp. 20 a small amount of an alcohol similar to, but not identical with, geraniol was obtained. The same alcohol was obtained previously from linalool and ethyl acetoacetate.

The acids obtained in exps. 21 and 22 were small in amount, gave no solid derivatives, and quickly resinified; hence accurate analysis was not possible. Good yields of unsaturated acids were obtained in exps. 23 and 24, cinnamylacetic acid being the main product in each case, and from the mother-liquors an oily acid was obtained which gave approximately the same equivalent and was probably a mixture of cinnamylacetic acid and β-phenyl-Δ^{γ}-pentenoic acid.

Apparently the active methylene group must have at least one adjacent carboxyl group, since with dibenzoylmethane and cinnamyl alcohol there was no addition at the double bond. Instead a good yield of acetophenone and cinnamyl benzoate was obtained.

EXPERIMENTAL.

Materials.—The preparation of the alcohols used in exps. 11—16 is described elsewhere, those used in exps. 7 and 8 were prepared by the Grignard reaction, and the remainder were high grade technical products. All were distilled before use. Ethyl butylacetoacetate was made from butyl bromide and ethyl acetoacetate.

Saturated Alcohols and Ethyl Acetoacetate.—*General procedure.* 1 G.-mol. each of the alcohol and ethyl acetoacetate and 1 g. of sodium acetate were heated slowly to 200—220° and maintained at this temperature for 3 hours. The distillate, mainly ethyl alcohol, contained some acetone and ethyl acetate. Carbon dioxide was evolved in every case. The residue was washed with dilute alkali solution to remove unchanged acetoacetate and distilled. The ester content of the whole distillate was determined by saponification with N/2-alcoholic potash. The distillate was hydrolysed with alkali, and the olefin and alcohol separated by fractional distillation. Titration with hydroxylamine solution showed no significant amount of ketone other than acetone.

Example : The first distillate from the benzyl alcohol experiment (No. 4) gave a mixture containing ethyl alcohol (0·95 mol.), acetone (0·11 mol.), and ethyl acetate (0·02 mol.). The second distillate (114 g.) contained 59% of benzyl acetate (= 0·46 mol.) and on hydrolysis gave 94 g. of benzyl alcohol (= 0·87 mol.).

Unsaturated Alcohols and Ethyl Acetoacetate.—The procedure was the same as above, except in exps. 9—12. It was necessary to reflux for a longer time to complete the alcoholysis. The ethyl alcohol formed was distilled off occasionally, and more of the unsaturated alcohol added to replace that lost by entrainment. When the theoretical amount of ethyl alcohol had distilled, the temperature was raised to 200°; pyrolysis then commenced and a mixture of alcohol, acetate, acetone, and unsaturated ketone distilled. The acetone was removed by fractional distillation, and the ester and ketone in the residue estimated as above.

Unsaturated Alcohols and Ethyl Butylacetoacetate.—Exp. 18. The methallyl ester was prepared by alcoholysis and then heated to 220° for 3 hours. During this time a mixture of methallyl alcohol (0·26 mol.), acetate (0·27 mol.), and methyl amyl ketone (0·10 mol.) distilled. On vacuum distillation the residue gave 0·26 mol. of methallyl hexoate and 22 g. of unchanged acetoacetate. No unsaturated ketone was found.

Exp. 19. The mixture was maintained at 240° for 5 hours after removal of ethyl alcohol (0·93 mol.). The residue was vacuum-distilled and gave methyl amyl ketone (0·15 mol.), a mixture of cinnamyl alcohol (0·2 mol.) and acetate (0·13 mol.), and a fraction, b. p. 150—170°, containing cinnamyl hexoate (0·39 mol.) and an unsaturated ketone. On hydrolysis this gave hexoic acid, cinnamyl alcohol, m. p. 30—32°, and the ketone, b. p. 155—160°/2 mm., which contained 91% of $C_{16}H_{22}O$, determined by titration with hydroxylamine.

Exp. 20. The reaction required only 2 hours at 210°, ethyl alcohol (0·9 mol.) distilling continuously during this time. The residue on distillation gave methyl amyl ketone (0·22 mol.), linalool (0·23 mol.), and an ester–ketone fraction, which on hydrolysis yielded hexoic acid (5 g.), an alcohol (21 g.), $C_{10}H_{18}O$, b. p. 95—101°/4 mm., $n_D^{20^\circ}$ 1·4750, and an unsaturated ketone (52 g.), b. p. 160—165°, $n_D^{20^\circ}$ 1·4708, $d_{4^\circ}^{20^\circ}$ 0·847, which contained 96% of $C_{13}H_{22}O$ (by titration).

Exps. 21 and 22. After the alcoholysis was complete, the temperature was maintained at 220—230° for 3 hours. A mixture of ethyl alcohol and acetate, unsaturated alcohol and acetate distilled during this time. The residue was hydrolysed by boiling with aqueous alkali and steam-distilled. The solution was acidified with excess of hydrochloric acid and boiled until carbon dioxide was no longer evolved. On extraction with ether the unsaturated acid was obtained. The acid from exp. 21 contained 93% of $C_5H_8O_2$ and that from exp. 22 96% of $C_6H_{10}O_2$ (titration). No solid derivatives could be obtained from either.

Exp. 23. 0·2 G.-mol. each of the alcohol and ethyl malonate and 0·5 g. of sodium acetate were heated at 200—230° for 3 hours; a total of 0·27 mol. of ethyl alcohol distilled. The residue was dissolved in 100 c.c. of alcohol, 30 c.c. of aqueous 40% sodium hydroxide solution added, the whole boiled for 2 hours and cooled, and the precipitate filtered off. The liquid was evaporated to dryness, the residue taken up in hot methanol and cooled, and the liquid filtered. The bulked solids were dissolved in water, excess of hydrochloric acid added, and the whole boiled. The acid obtained (13 g.) had m. p. 90—91° after crystallisation (Found : *M*, by alkali titration, 179. Calc. for cinnamylacetic acid : *M*, 176). This acid, prepared for comparison from cinnamyl chloride and ethyl malonate, had m. p. 91—91·5°, mixed m. p. 90—91°. By the same treatment the methyl-alcoholic filtrate gave an oily acid (10 g.) (Found : *M*, 180), which on oxidation with alkaline permanganate gave benzoic acid, probably formed from the cinnamylacetic acid still present.

Exp. 24. With the same conditions and quantities as in exp. 23, 0·26 mol. of ethyl alcohol distilled, and the solid acid (15 g.) had m. p. 89—90°, mixed m. p. 90—91°. 5 G. of the oily acid were obtained.

Benzyl Alcohol and Butyl Malonate.—0·5 G.-mol. of each and 2 g. of sodium acetate were heated at 220—230° for 6 hours; during this time butyl alcohol (0·61 mol.) and acetate (0·11 mol.) distilled. The residue yielded 5 g. of an oily acid, which on distillation gave β-phenylpropionic acid, m. p. 45—47° (anilide, m. p. 96—97°).

Dibenzoylmethane and Cinnamyl Alcohol.—0·1 Mol. of the diketone and 0·165 mol. of the alcohol gave 0·083 mol. of acetophenone, 0·082 mol. of cinnamyl alcohol, and 0·072 mol. of cinnamyl benzoate.

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