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Aldol Reactions of Formaldehyde in Non-aqueous Media

VII.* Acid-catalyzed Reaction of β-Keto Esters with Formaldehyde

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Reactions of some β-keto esters with formaldehyde in refluxing chloroform and with boron trifluoride as a catalyst have been shown to yield 5-acyl-5-alkoxycarbonyl-1,3-dioxanes. Ethyl 2-benzoylacrylate was found to be an intermediate in the formation of 5-benzoyl-5-ethoxycarbonyl-1,3-dioxane from ethyl benzoylacetate. In addition to 1,3-dioxanes, ethyl acetoacetate and ethyl butyrylacetate also yielded the corresponding 3-acyl-6-alkyl-3,5-bis(ethoxycarbonyl)-2,3-dihydro-4*H*-pyranes and 3,5-diacyl-3,5-bis(ethoxycarbonyl)-tetrahydropyranes, the former compounds being intermediates in the formation of the latter ones.

β-Keto esters are stronger acids [1] and more enolized [2] than simple ketones due to the strong activation of the α-hydrogen atoms by the two carbonyl groups,[2] and especially in non-polar solvents the enol forms are favoured due to strong intramolecular hydrogen bonding.[3] The acidity and high enol contents of the esters make aldol reactions possible under very mild conditions. Thus, according to Rabe and Rahm,[4] the reaction of ethyl acetoacetate with aqueous formaldehyde at room temperature and without any catalyst gives a high yield of methylene bis(ethyl acetoacetate) (*1*). This compound is also formed when either piperidine or dimethyl amine is used as catalyst, but with these catalysts the reaction is easily carried further with formation of the cyclohexenone derivative *2*.[5] The use of alkaline catalysts also gives rise to the unsaturated compound *4* (R=H),[6] formed *via* the intermediate hydroxymethyl compound *3* (R=H), which is reported to be very unstable, suffering dehydration even at low temperatures.[6] Aldol reactions of ethyl acetoacetate with higher aldehydes yield stable hydroxylic compounds (*3*).[6]

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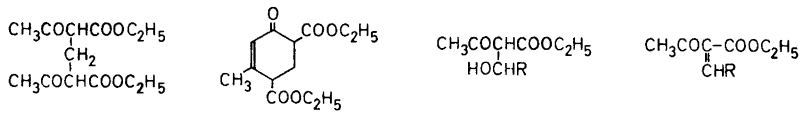
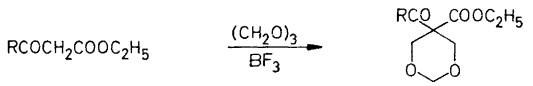


1 2 3 4



5: R=CH_3
6: R=$CH_3CH_2CH_2$
7: R=$(CH_3)_2CH$

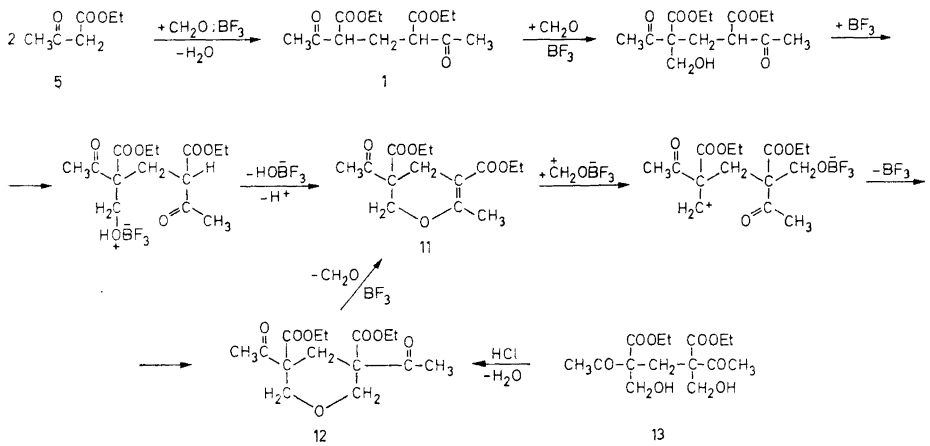
8: R=CH_3
9: R=$CH_3CH_2CH_2$
10: R=$(CH_3)_2CH$

So far, nothing apparently has been reported about acid-catalyzed aldol reactions of formaldehyde with β-keto esters, but benzaldehyde and higher aliphatic aldehydes have been shown to react with ethyl acetoacetate in the presence of hydrogen chloride with formation of unsaturated compounds of the type *4*.[7] In the present paper acid-catalyzed aldol reactions between formaldehyde and some β-keto esters are described, and mechanisms for the reactions are proposed.

RESULTS AND DISCUSSION

Aldehydes and ketones with α-methylene groups react with formaldehyde in refluxing chloroform under the influence of acid catalysts with the formation of 1,3-dioxanes.[8–10] Thus, it was not surprising to find that the β-keto esters *5*—*7*, which contain methylene groups activated by two carbonyl groups,

SCHEME 1



react readily with trioxane (1 mole per mole of ester) in refluxing chloroform and in the presence of boron trifluoride etherate to yield the 5-acetyl-5-ethoxycarbonyl-1,3-dioxanes *8*—*10*, respectively. The reaction of ethyl acetoacetate (*5*) yielded, in addition to the 1,3-dioxane mentioned above, a higher-boiling compound, which was characterized as 3,5-diacetyl-3,5-bis(ethoxycarbonyl)tetrahydropyrane (*12*) (the NMR spectrum of *12* is given in Fig. 3). This compound has previously been obtained by Décombe [11] on treatment of the symmetric bis(hydroxymethyl) derivative *13* (Scheme 1) with hydrochloric acid.

An increase of the molar ratio β-keto ester/trioxane to 2:1 resulted in the formation of a third major reaction product, which was assigned structure *11*, *i.e.* 3-acetyl-6-methyl-3,5-bis(ethoxycarbonyl)-2,3-dihydro-4*H*-pyrane. A comparison of the time-yield curves for the dihydropyrane *11* and the tetrahydropyrane *12* (Fig. 1) suggested that *11* was an intermediate in the formation of *12*. In fact, treatment of isolated dihydropyrane *11* with trioxane and boron trifluoride etherate in refluxing chloroform gave the tetrahydropyrane *12*; this reaction was found to be reversible.

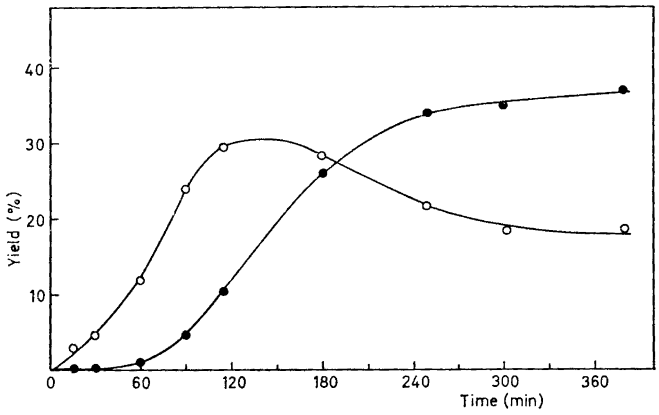
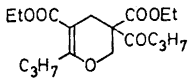


Fig. 1. Formation of dihydropyrane *11* (○) and tetrahydropyrane *12* (●) from ethyl acetoacetate (*5*) and formaldehyde in refluxing chloroform and with boron trifluoride etherate as a catalyst.

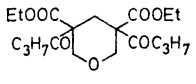
Dihydropyrane *11* can be regarded as an intramolecular enol ether of the monohydroxymethyl derivative of methylene bis(ethyl acetoacetate) (*1*), the latter compound thus being a likely intermediate in the formation of *11* from ethyl acetoacetate and formaldehyde. In accordance with this view, a mixture of compounds *11* and *12* was obtained on treatment of the methylene compound *1* with trioxane in refluxing chloroform and with boron trifluoride etherate as a catalyst. A reaction path for the formation of *11* and *12* from ethyl acetoacetate and formaldehyde is proposed in Scheme 1. The last step in the reaction sequence, *i.e.* the formation of tetrahydropyrane *12* from *11*, is believed to involve an electrophilic addition of the conjugate acid of form-

aldehyde to the double bond of the enol ether *11* with opening of the dihydropyrane ring. The primary carbonium ion formed may then be attacked by the oxygen atom of the hydroxymethyl group with closure of the tetrahydropyrane ring.

A homologue of compound *11*, the dihydropyrane *14* (the NMR spectrum of *14* is given in Fig. 4), was obtained in a fair yield together with minor amounts of 1,3-dioxane *9* when ethyl butyrylacetate (*6*) was allowed to react in refluxing chloroform with trioxane (0.5 mole per mole of ester) and boron



14

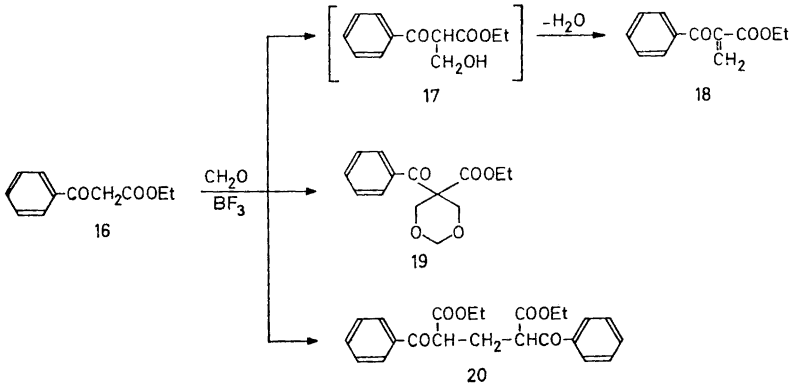


15

trifluoride etherate. No appreciable amounts of other volatile products were formed. The isolated dihydropyrane *14*, however, was shown to react rapidly with an excess of formaldehyde to give the tetrahydropyrane *15*. Compound *15* apparently was less stable than its lower homologue (*12*) and was consumed on prolonged reaction with formaldehyde.

In addition to the expected 1,3-dioxane *19* (Scheme 2), ethyl 2-benzoylacrylate (*18*) was formed in the reaction of ethyl benzoylacetate (*16*) with formaldehyde in the presence of boron trifluoride etherate. A small amount

SCHEME 2



of a third product, methylene bis(ethyl benzoylacetate) (*20*) crystallized from the reaction mixture on standing. The unsaturated ester *18* was shown by vapour phase chromatography to be the primary reaction product, formed in a very rapid reaction. The 1,3-dioxane *19* was formed in a slower reaction with the simultaneous consumption of *18* (Fig. 2). This observation indicated that the acrylate *18* may have been an intermediate in the formation of 1,3-dioxane *19*, and this hypothesis was supported by treatment of compound *18* with

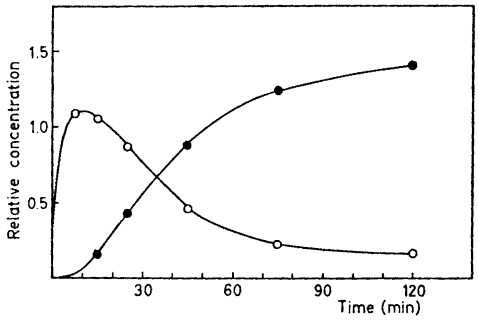
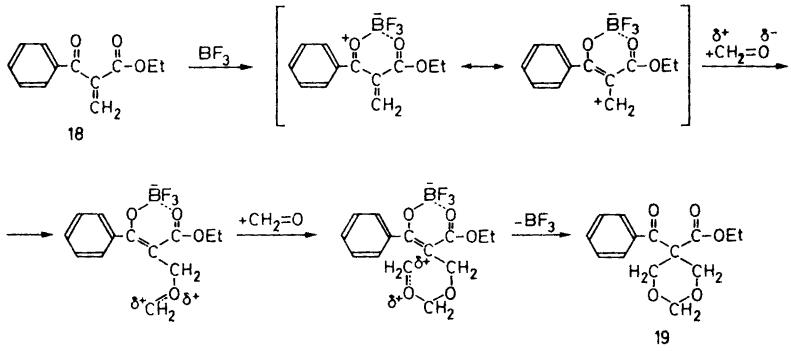


Fig. 2. Formation of ethyl 2-benzoylacrylate (*18*, ○) and 5-benzoyl-5-ethoxycarbonyl-1,3-dioxane (*19*, ●) from ethyl benzoylacetate (*16*) and formaldehyde in refluxing chloroform and with boron trifluoride etherate as a catalyst.

trioxane and boron trifluoride etherate in refluxing chloroform, which yielded 1,3-dioxane *19* as the only volatile product.

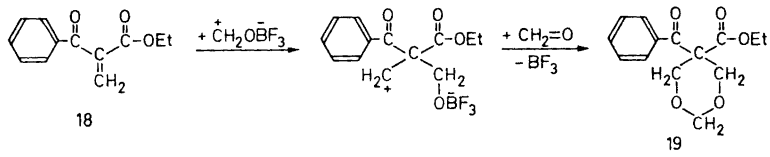
This experiment did not, however, entirely rule out the possibility that the unsaturated compound *18* and the very small amount of water present in the solvent were in equilibrium with the hydroxymethyl compound *17* under the conditions used, and that this compound on reaction with formaldehyde gave rise to the 1,3-dioxane *19*. If this was the case, addition of water to the solvent should have inreased the rate of formation of 1,3-dioxane *19* from com-

SCHEME 3



pound *18* and formaldehyde. Saturation of the chloroform with water did not, however, appreciably change the reaction rate; therefore it seems more likely that the 1,3-dioxane *19* was formed *via* the unsaturated compound *18*, by a mechanism entirely different from that reported previously for the formation of 5-acetyl-5-methyl-1,3-dioxane from 2-butanone.[9] The reaction of the α,β-unsaturated ketone *18* with formaldehyde to yield 1,3-dioxane *19* may be understood either to be a 1,4-addition of the conjugate acid of formaldehyde, *i.e.* addition of boron trifluoride at the carbonyl group, and of formaldehyde at the β-carbon atom (Scheme 3), or a Prins reaction (Scheme 4),[12] and will be discussed in a further communication together with reactions of other α,β-unsaturated carbonyl compounds with formaldehyde in the chloroform-BF_3 system.

SCHEME 4



18 19

EXPERIMENTAL

Trioxane was supplied by Perstorp AB, Perstorp, Sweden. Commercial organic *purum* grade chemicals were usually distilled before use. IR spectra were recorded on a Beckman IR-9 spectrophotometer, and NMR spectra on a Varian A-60 instrument. Vapour phase chromatography (VPC) was performed using a Perkin-Elmer 800 instrument. Boiling and melting points are uncorrected.

Reaction of ethyl acetoacetate (5) *with formaldehyde.* A. A solution of ethyl acetoacetate (13.0 g, 0.10 mole) and trioxane (9.0 g, 0.10 mole) in chloroform (300 ml) was heated to reflux, and boron trifluoride etherate (7.0 g, 0.05 mole) was added. The solution was refluxed for 60 min with continuous removal of water. After the solution had been washed with water and neutralized with sodium bicarbonate the solvent was removed under reduced pressure. The residue was distilled *in vacuo* to yield 5-acetyl-5-ethoxycarbonyl-1,3-dioxane (*8*)—main fraction b.p.$_{2.4}$ 117—120°. (Found: C 53.27; H 7.05. Calc. for $C_9H_{14}O_5$: C 53.46; H 6.98) — and 3,5-diacetyl-3,5-bis(ethoxycarbonyl)tetrahydropyrane (*12*) — main fraction b.p.$_{3.0}$ 165—170°, m.p. 88—89° (lit.[11] 89—90°). (Found: C 57.23; H 7.05. Calc. for $C_{15}H_{22}O_7$: C 57.32; H 7.06). The yields of the products were determined by VPC

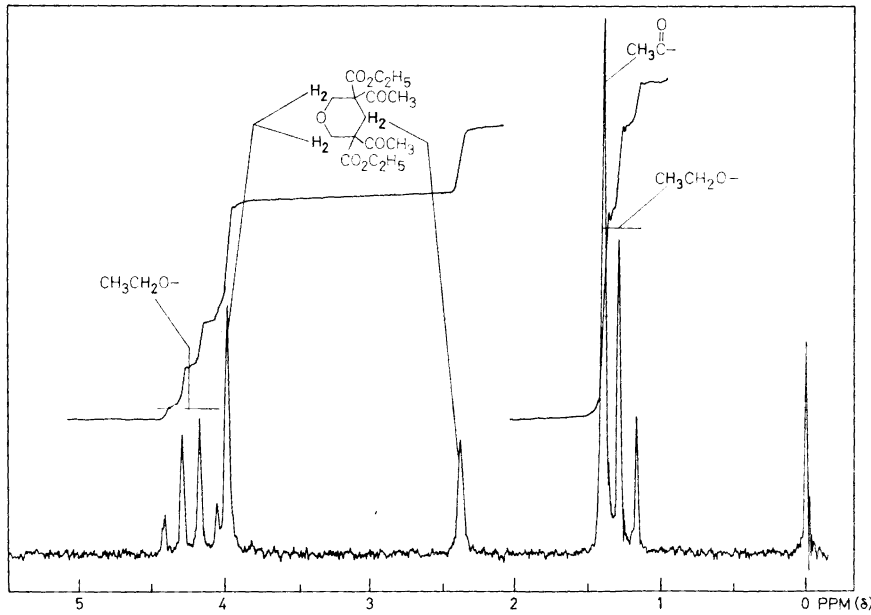


Fig. 3. NMR spectrum of 3,5-diacetyl-3,5-bis(ethoxycarbonyl)tetrahydropyrane (*12*).

of the reaction mixture to be 7.6 g (38 %) and 8.2 g (52 %), respectively. IR and NMR spectra (the NMR spectrum of *12* is given in Fig. 3) were consistent with the assigned structures.

B. A solution of ethyl acetoacetate (65 g, 0.5 mole) and trioxane (22.5 g, 0.25 mole) in chloroform (75 ml) was heated to reflux, and boron trifluoride etherate (3.5 g, 0.025 mole) was added. The solution was refluxed for 3 h with continuous removal of water. The reaction mixture was worked up as described under A and distilled *in vacuo* to give 15 g of pure tetrahydropyrane *12* and 17 g of a mixture (b.p.$_{2.4}$ 169–172°), containing (as shown by VPC) 30 % of *12* and 70 % of a compound, which after repeated chromatography on silica gel (eluent benzene-ethyl acetate 4:1) was characterized as 3-acetyl-6-methyl-3,5-bis(ethoxycarbonyl)-2,3-dihydro-4*H*-pyrane (*11*). (Found: C 58.71; H 7.05. Calc. for $C_{14}H_{20}O_6$: C 59.14; H 7.09). IR spectrum (all strong absorptions): 1710 cm^{-1}

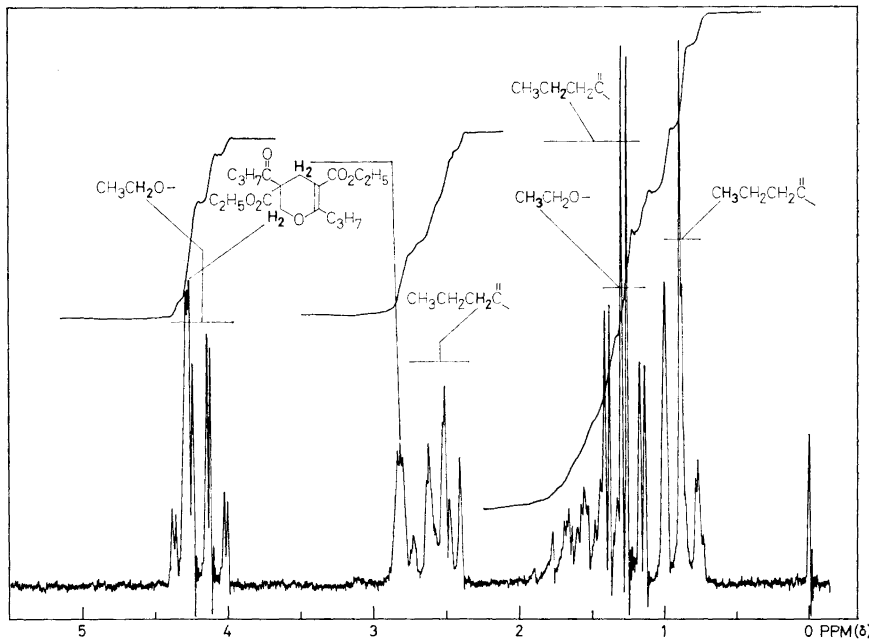


Fig. 4. NMR spectrum of 3-butyryl-6-propyl-3,5-bis(ethoxycarbonyl)-2,3-dihydro-4*H*-pyrane (*14*).

with a shoulder at 1735 cm^{-1}, ketone and ester carbonyls; 1630 cm^{-1}, double bond of enol ether. NMR spectrum (*cf.* Fig. 4): 1.27 ppm, triplet, and 4.22 ppm, quartet, CH_3CH_2O-; 1.31 ppm, triplet, and 4.26 ppm, quartet, CH_3CH_2O-; 2.20 ppm, triplet, $CH_3C(=C)-O-$; 2.24 ppm, singlet, $CH_3C(=O)-$; 2.84 ppm, broad unresolved multiplet, $C-CH_2-C$; and 4.31 ppm, singlet, $C-CH_2-O$. UV spectrum: $\lambda_{max}=241$ mμ, $\log \varepsilon_{max}=3.96$; $\lambda_{infl.}=286$ mμ, $\log \varepsilon_{infl.}=2.10$. The compound was easily oxidized by aqueous potassium permanganate.

C. In an experiment similar to that described under B, samples of the reaction mixture were collected 15, 30, 60, 90, 120, 180, 250, 300, and 370 min after addition of the catalyst and neutralized with sodium bicarbonate, and the yields of compounds *11* and *12* determined by VPC. Results are given in Fig. 1.

Treatment of dihydropyrane 11 *with formaldehyde.* A solution of compound *11* (0.4 g, 1.4 mmoles) and trioxane (0.5 g, 5.5 mmoles) in chloroform (25 ml) was heated to reflux, and boron trifluoride etherate (1 ml) was added. After 10 min a sample was neutralized with sodium bicarbonate and analyzed by VPC. The main product, tetrahydropyrane *12*, was found in a yield of 0.18 g (41 %). All starting material was consumed.

Treatment of tetrahydropyrane 12 *with boron trifluoride etherate.* A solution of tetrahydropyrane *12* (6.1 g, 1.9 mmoles) in chloroform (40 ml) was heated to reflux and boron trifluoride etherate (1.25 ml) was added. After 18 h reaction a deposit of paraformaldehyde in the reflux condenser was detected. A sample of the reaction mixture was neutralized with sodium bicarbonate and analyzed by VPC. Dihydropyrane *11* (2.5 g, 45 % yield) was found, together with 1.2 g of unchanged starting material.

Reaction of methylene bis(ethyl acetoacetate) (1) *with formaldehyde.* A solution (100 ml) of methylene bis(ethyl acetoacetate) (*1*; 5.44 g, 20 mmoles), prepared according to Rabe and Rahm,[4] and trioxane (1.18 g, 13.3 mmoles) in chloroform was heated to reflux, and boron trifluoride etherate (3 ml) was added. Water was removed continuously. After 60 min reaction the solution was washed with water and neutralized with sodium bicarbonate. After the solution had been dried over anhydrous calcium sulfate the solvent was removed under reduced pressure to give 5.7 g of a yellow, partially crystalline residue, which was shown by VPC and thin layer chromatography to consist of equal parts of compounds *11* and *12*.

Reaction of ethyl butyrylacetate (6) *with formaldehyde.* A. Ethyl butyrylacetate (*6*) was allowed to react with formaldehyde under similar conditions as ethyl acetoacetate (*5*: item A). After distillation *in vacuo* (main fraction, $b.p._{1.5}$ 125—128°) and chromatography on silica gel (eluent benzene-isopropyl ether 4:1) 5-butyryl-5-ethoxycarbonyl-1,3-dioxane (*9*) was obtained. (Found: C 57.35; H 7.86. Calc. for $C_{11}H_{18}O_5$: C 57.38; H 7.88). IR and NMR spectra were consistent with the assigned structure. Yield 34 %.

B. Ethyl butyrylacetate (*6*) was allowed to react with formaldehyde under similar conditions as ethyl acetoacetate (*5*; item B). Distillation *in vacuo* gave a series of fractions (main fraction, $b.p._{2.2}$ 175—196°), which according to VPC contained a total of 21.5 g (25 %) of 3-butyryl-6-propyl-3,5-bis(ethoxycarbonyl)-2,3-dihydro-4*H*-pyrane (*14*). The compound was purified by chromatography on silica gel, eluent benzene-isopropyl ether 4:1 (Found: C 63.52; H 8.06. Calc. for $C_{18}H_{28}O_6$: C 63.51; H 8.29). IR and NMR spectra (NMR spectrum of *14* is given in Fig. 4) were consistent with the assigned structure.

Treatment of dihydropyrane 14 *with formaldehyde.* A solution of dihydropyrane *14* (10.2 g, 30 mmoles), trioxane (5.4 g, 60 mmoles), and boron trifluoride etherate (2.0 ml) in chloroform (75 ml) was refluxed for 20 min. The reaction mixture was washed with water, neutralized with sodium bicarbonate and dried over anhydrous calcium sulfate. The solvent was removed under reduced pressure to yield 13.8 g of a yellow oil. Distillation *in vacuo* gave 4.2 g of a mixture ($b.p._{1.7}$ 170—210°) of equal amounts of the starting material and a compound, which after purification by repeated chromatography on silica gel (eluent benzene-isopropyl ether 4:1) was characterized as 3,5-dibutyryl-3,5-bis(ethoxycarbonyl)tetrahydropyrane (*15*) by IR and NMR spectra. (Found: C 62.21; H 7.92. Calc. for $C_{19}H_{30}O_7$: C 61.60; H 8.16). IR spectrum: 1729 cm^{-1} and 1738 cm^{-1}, ketone and ester carbonyls. NMR spectrum: 1.27 ppm, triplet, and 4.19 ppm, quartet, CH_3CH_2O-; 0.90 ppm, triplet (distorted), and 1.55 ppm (*ca.*), multiplet, $CH_3CH_2CH_2CO-$; 2.35 ppm, singlet, $C-CH_2-C$; 3.94 ppm, singlet, $C-CH_2-O$. With the exception of the signals from the butyryl groups, the spectrum is similar to that of tetrahydropyrane *12* (Fig. 3).

Reaction of ethyl isobutyrylacetate (7) *with formaldehyde.* Ethyl isobutyrylacetate (*7*) was allowed to react with formaldehyde under similar conditions as ethyl acetoacetate (*5*; item A). After distillation *in vacuo* (main fraction $b.p._{0.4}$ 89—101°), 5-isobutyryl-5-ethoxycarbonyl-1,3-dioxane (*10*) was obtained. (Found: C 57.26; H 7.87. Calc. for $C_{11}H_{18}O_5$: C 57.38; H 7.88). IR and NMR spectra were consistent with the assigned structure. Yield 36 %.

Reaction of ethyl benzoylacetate (16) *with formaldehyde.* A solution of ethyl benzoylacetate (19.4 g, 0.1 mole), trioxane (9.0 g, 0.1 mole), and boron trifluoride etherate (3.0 g, 0.021 mole) in chloroform (100 ml) was refluxed for 60 min with continuous removal of water. The reaction mixture was washed with water, neutralized with sodium bicarbonate and dried over anhydrous calcium sulfate. Removal of the solvent under reduced

pressure gave 22.9 g of a yellow oil. Chromatography on silica gel (eluent benzene-isopropyl ether 4:1) of 2.01 g of this oil gave two groups of fractions, which on evaporation of the solvent gave the following products:

1) 0.57 g of a colourless oil, which polymerized to a soft resin unless a stabilizing agent such as hydroquinone was added. The oil decolorized aqueous potassium permanganate as well as a carbon tetrachloride solution of bromine. IR and NMR spectra of the oil indicated that it consisted of ethyl 2-benzoylacrylate (*18*). Yield, 32 %. IR spectrum: 1730 cm^{-1} (strong), conjugated ester carbonyl; 1680 cm^{-1} (strong), conjugated ketone carbonyl; 1630 cm^{-1} (weak), conjugated double bond. NMR spectrum: 1.18 ppm, triplet, and 4.22 ppm, quartet, CH_3CH_2O-; 6.06 ppm, singlet, and 6.68 ppm, singlet, $CH_2=C<$; 7.5 ppm, multiplet, and 7.9 ppm, multiplet, C_6H_5-.

VPC as well as thin layer chromatography revealed the presence of small amounts of impurities. Attempts to obtain a completely pure product by distillation *in vacuo* followed by chromatography on silica gel were unsuccessful. (Found: C 69.84; H 6.00. Calc. for $C_{12}H_{12}O_3$: C 70.57; H 5.92).

2) 0.71 g of a colourless oil, which according to IR and NMR spectra consisted of 5-benzoyl-5-ethoxycarbonyl-1,3-dioxane (*19*). (Found: C 63.38; H 6.13. Calc. for $C_{14}H_{16}O_5$: C 63.62; H 6.10). Yield, 31 %.

The crude reaction product partially crystallized on standing, and after recrystallization from petroleum ether-isopropyl ether 1:1, a small amount of colourless crystals of methylene bis(ethyl benzoylacetate) *20*, m.p. 91–92° (lit.[13] 92.5°), was obtained. IR and NMR spectra were consistent with the assigned structure. (Found: C 69.64; H 6.07.Calc. for $C_{23}H_{24}O_6$: C 69.69; H 6.06).

B. A solution of ethyl benzoylacetate (9.5 g, 50 mmoles) and trioxane (6 g, 67 mmoles) in chloroform (100 ml) was heated to reflux, and boron trifluoride etherate (3 g, 21 mmoles) was added. Water was removed continuously by a water trap. Samples were withdrawn 7.5, 15, 25, 45, and 75 min after the addition of the catalyst, neutralized with sodium bicarbonate and analyzed by VPC. In Fig. 2 the peak areas of ethyl 2-benzoylacrylate (*18*) and 5-benzoyl-5-ethoxycarbonyl-1,3-dioxane (*19*) are given in relation to the peak area of an internal standard (fluorene).

Treatment of ethyl 2-benzoylacrylate (18) *with formaldehyde.* A. A solution (50 ml) of ethyl 2-benzoylacrylate (1.5 g, 7.4 mmoles) and trioxane (1.5 g, 16.7 mmoles) in chloroform (freshly distilled over P_2O_5) was heated to reflux, and boron trifluoride etherate (2 ml) was added. Samples were withdrawn 5, 12, and 20 min after addition of the catalyst, neutralized with sodium bicarbonate and analyzed by VPC. The following amounts of compound *18* were found: 5 min, 4.0 mmoles; 12 min, 2.7 mmoles; 20 min, 2.3 mmoles. The only reaction product observable by VPC was found to be 5-benzoyl-5-ethoxycarbonyl-1,3-dioxane (*19*) in the following amounts: 5 min, 1.4 mmoles; 12 min, 1.8 mmoles; 20 min, 2.1 mmoles.

B. In an experiment similar to A with chloroform saturated with water as a solvent, the following amounts of compound *18* were found: 5 min, 3.6 mmoles; 12 min, 2.4 mmoles; 20 min, 2.0 mmoles. The reaction product *19* was found in the following amounts: 5 min, 1.4 mmoles; 12 min, 1.8 mmoles; 20 min, 2.0 mmoles.

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