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# Aldol Reactions of Formaldehyde in Non-aqueous Media

## III.* Acid-catalyzed Reaction of Aldehydes and Ketones with Formaldehyde

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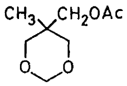
Reactions of formaldehyde with aldehydes and ketones in refluxing chloroform solution and in the presence of sulfuric acid, boron trifluoride etherate, or aluminium chloride yielded 5-acyl-5-alkyl-1,3-dioxanes. From aldehydes, 1-alkyl-bicyclo[4.4.0]-3,5,7,9-tetraoxadecanes were obtained in addition to the 1,3-dioxanes.

Acid-catalyzed aldol reactions of aldehydes and ketones have been known for a long time. It has been assumed[1] that the first step in the reaction is the protonation of the carbonyl group to form the conjugate acid of the carbonyl compound, which reacts with the enol of the same or another carbonyl compound in an electrophilic addition to give a $\beta$-ketol. The $\beta$-ketol may undergo an acid-catalyzed dehydration to yield an $\alpha,\beta$-unsaturated ketone. This reaction mechanism was supported by Noyce *et al.*,[2] who found that in the reaction of anisaldehyde with 2-butanone in a mixture of acetic acid and sulfuric acid a rapid enolization of 2-butanone was followed by a slow addition of the conjugate acid of the aldehyde to the enol.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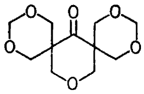
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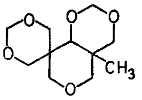
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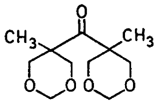
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* Part II: *Acta Chem. Scand.* **21** (1967) 718.

Olsen *et al.*[3,4] have shown that formaldehyde reacts with aldehydes and ketones in a mixture of acetic acid and sulfuric acid. Under the conditions used propionaldehyde yielded 5-acetoxymethyl-5-methyl-1,3-dioxane (*1*), in which the original aldehyde group had undergone reduction,[3] and acetone gave compound *2*. Under similar conditions, Wöllner *et al.*[5,6] obtained compounds *3* and *4* from 2-butanone and 3-pentanone, respectively.

*Table 1.* Starting materials, products and yields in the reaction of trioxane with aldehydes and ketones in the presence of acid catalysts.

| Carbonyl compound | Molar ratio trioxane/carbonyl compound | | | Products | Yields, % [a] | | |
|---|---|---|---|---|---|---|---|
| | $H_2SO_4$ | $BF_3$-etherate | $AlCl_3$ | | $H_2SO_4$ | $BF_3$-etherate | $AlCl_3$ |
| Propionaldehyde | 1.67 | 1.67 | | *5* | 10 | 7 | |
| | | | | *32* | 40 | 37 | |
| Butyraldehyde | 1.67 | 1.67 | | *6* | 20 | 22 | |
| | | | | *33* | 35 | 33 | |
| Valeraldehyde | 1.67 | 1.67 | | *7* | 35 | 39 | |
| | | | | *34* | 30 | 33 | |
| Isovaleraldehyde | 1.33 | 1.33 | | *8* | 49 | 40 | |
| | | | | *35* | 13 | 10 | |
| Acetone | 0.5 | 0.5 | 1.33 | *9* | 3 | 36 | 3 |
| 2-Butanone | 0.5 | 0.5 | 1.33 | *10*[8] | 98 | 68 | 50 |
| 2-Pentanone | 0.5 | 0.5 | 1.33 | *11* | 80 | 56 | 21 |
| 2-Hexanone | 0.5 | 0.5 | 1.33 | *12* | 79 | 61 | 29 |
| 4-Methyl-2-pentanone | 0.5 | 0.5 | 1.33 | *13* | 37 | 33 | 12 |
| | | | | *14* | 6 | 33 | 2 |
| | | | | *15* | | | 7 |
| 4,4-Dimethyl-2-pentanone | 0.9 | 1.0 | 1.33 | *16* | 6 [b] | 32 [b] | |
| | | | | *17* | | | 9 [b] |
| 3-Pentanone | 0.5 | 0.5 | 1.33 | *18* | 80 | 72 | 30 |
| 3-Hexanone | 0.9 | | | *19* | 43 [b] | | |
| | | | | *20* | 16 [b] | | |
| 3-Heptanone | 0.5 | 0.5 | 1.33 | *21* | 69 | 54 | 31 |
| | | | | *22* | 23 | 18 | 10 |
| 5-Methyl-3-hexanone | 0.5 | 0.5 | 1.33 | *23* | 76 | 72 | 39 |
| 3-Octanone | 0.9 | | | *24* | 47 [b] | | |
| | | | | *25* | 16 [b] | | |
| 2,6-Dimethyl-4-heptanone | 0.5 | 0.5 | 1.33 | *26* | 38 | 49 | 11 |
| Acetophenone | 1.33 | 0.5 | | *27*[9] | 19 [b] | 82 | |
| Propiophenone | 0.67 | | 0.67 | *28* | 84 [c] | | 84 [c] |
| Benzyl methyl ketone | | 1.1 | 1.0 | *29* | | 54 [b] | 20 [b] |
| Benzyl phenyl ketone | | 1.1 | | *30* | | 70 [c] | |
| Cyclopentanone | | 0.95 | 0.95 | *31* | | 10 [b] | 5 [b] |

[a] Yields are based on the reactant present in the least amount, and are determined by VPC except where otherwise noted.

[b] Yields determined after distillation.

[c] Yield of crude crystalline product.

As reported in a preliminary communication [7] it has now been found that aldehydes and ketones containing an α-methylene group react readily with formaldehyde in refluxing chloroform solution and in the presence of acid catalysts, 5-acyl-5-alkyl-1,3-dioxanes being formed. From aldehydes 1-alkylbicyclo[4.4.0]-3,5,7,9-tetraoxadecanes were obtained in addition to the 1,3-dioxanes. In the present paper, the reactions of formaldehyde with 4 different aldehydes and 17 different ketones are reported, and a reaction path is proposed. In unsymmetrical ketones, such as methyl alkyl ketones, reaction at either one of the two α-positions leads to two isomeric 1,3-dioxanes; the factors governing the preferred formation of one of these isomers are discussed.

## RESULTS AND DISCUSSION

The reactions were carried out in refluxing chloroform solution and in the presence of three different catalysts, *viz.* sulfuric acid, boron trifluoride etherate, and aluminium chloride. Formaldehyde was generated *in situ* by the acid-catalyzed depolymerization of trioxane, the cyclic formaldehyde trimer. Starting materials, products and yields are summarized in Table 1.

When aluminium chloride was used as a catalyst in the reactions of ketones with trioxane lower yields of 1,3-dioxanes generally were obtained than with the two other catalysts used. This was due to incomplete reaction, since considerable amounts of ketone were found to be unconsumed after the reaction.

Table 2 shows the results of a series of experiments in which butyraldehyde was allowed to react with trioxane under various conditions. An increase of the trioxane content (run 2) over that calculated for the formation of *33* (0.67 mole, run 1) did not affect the yields of the products. The concentration of the catalyst was found to have a great influence on the reaction rates (Fig. 1) but the final yields were not affected. The yields of the products were only slightly dependent on the amount of solvent used (runs 3—5). Higher dilution gave somewhat higher yields, indicating decreased formation of by-products. The by-products were found largely to consist of polymeric material, remaining as viscous oils or resins after volatile matter had been distilled off. Vapour phase chromatography revealed only minor amounts of volatile by-products.

*Table 2.* Reaction of butyraldehyde with trioxane.

| Run No. | Butyraldehyde moles | Trioxane moles | $BF_3$-etherate moles | $CHCl_3$ ml | Time h | Yield, % [a] | |
|---|---|---|---|---|---|---|---|
| | | | | | | *6* | *33* |
| 1 | 0.5 | 0.67 | 0.075 | 250 | 5 | 22 | 29 |
| 2 | 0.5 | 1.00 | 0.075 | 250 | 5 | 21 | 30 |
| 3 | 0.5 | 0.67 | 0.075 | 150 | 4 | 22 | 24 |
| 4 | 0.5 | 0.67 | 0.075 | 350 | 4 | 23 | 32 |
| 5 | 0.5 | 0.67 | 0.075 | 500 | 4 | 25 | 30 |

[a] Yields are determined by VPC and are based on the amount of butyraldehyde used.

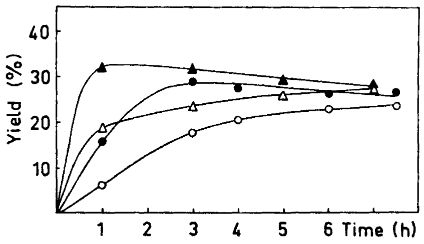


*Fig. 1.* The formation of 1,3-dioxane *6* and bicyclotetraoxadecane *33* from butyraldehyde (0.5 mole) and trioxane (0.67 mole) in chloroform (350 ml). With 0.05 mole of boron trifluoride etherate: *6* (○), *33* (●); with 0.15 mole of boron trifluoride etherate: *6* (△), *33* (▲).

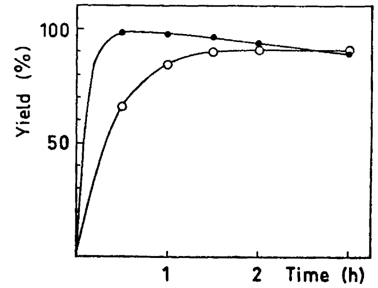
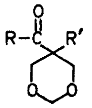
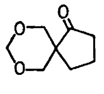


*Fig. 2.* The formation of 1,3-dioxane *10* from 2-butanone (0.5 mole) and trioxane (0.25 mole) in chloroform (100 ml) under the influence of 2 ml of $H_2SO_4$ (○) and 4 ml of $H_2SO_4$ (●).

The reaction of 2-butanone with trioxane in the presence of sulfuric acid was also studied more extensively in order to determine optimum conditions for the formation of 5-acetyl-5-methyl-1,3-dioxane (*10*). A series of experiments with varying amounts of reactants, catalyst and solvent was carried out, and the results are presented in Table 3 and Fig. 2. The formation of *10* was found to be favoured by a low molar ratio of trioxane/ketone (runs



5: R = H; $R'=CH_3$
6: R = H; $R'=C_2H_5$
7: R = H; $R'=C_3H_7$
8: R = H; $R'=CH(CH_3)_2$
9: R = $CH_3$; R'=H
10: R = $R'=CH_3$
11: R = $CH_3$; $R'=C_2H_5$
12: R = $CH_3$; $R'=C_3H_7$
13: R = $CH_3$; $R'=CH(CH_3)_2$
14: R = $CH_2CH(CH_3)_2$; R'=H
15: R = $CH_2CH(CH_3)_2$; $R'=CH_2Cl$
16: R = $CH_2C(CH_3)_3$; R'=H
17: R = $CH_2C(CH_3)_3$; $R'=CH_2Cl$
18: R = $C_2H_5$; $R'=CH_3$
19: R = $C_3H_7$; $R'=CH_3$
20: R = $R'=C_2H_5$
21: R = $C_4H_9$; $R'=CH_3$
22: R = $C_2H_5$; $R'=C_3H_7$
23: R = $CH_2CH(CH_3)_2$; $R'=CH_3$
24: R = $C_5H_{11}$; $R'=CH_3$
25: R = $C_2H_5$; $R'=C_4H_9$
26: R = $CH_2CH(CH_3)_2$; $R'=CH(CH_3)_2$
27: R = $C_6H_5$; R'=H
28: R = $C_6H_5$; $R'=CH_3$
29: R = $CH_3$; $R'=C_6H_5$
30: R = $R'=C_6H_5$



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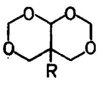


32: $R=CH_3$
33: $R=C_2H_5$
34: $R=C_3H_7$
35: $R=CH(CH_3)_2$

*Table 3.* Reaction of 2-butanone with trioxane.

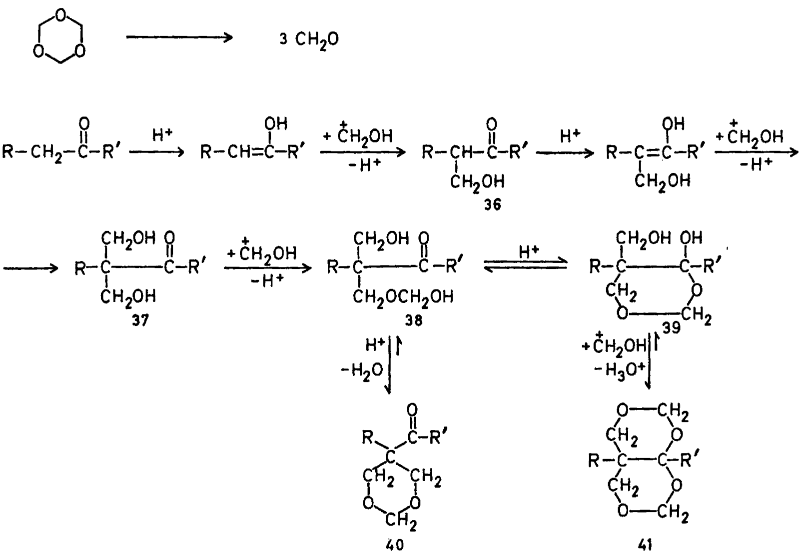
| Run No. | 2-Butanone moles | Trioxane moles | $H_2SO_4$ ml | $CHCl_3$ ml | Time h | Yield of *10* % [a] |
|---|---|---|---|---|---|---|
| 1 | 0.5 | 0.13 | 2 | 100 | 3 | 83 |
| 2 | 0.5 | 0.25 | 2 | 100 | 3 | 89 |
| 3 | 0.5 | 0.50 | 2 | 100 | 3 | 69 |
| 4 | 1.0 | 0.25 | 2 | 110 [b] | 3 | 85 |
| 5 | 2.0 | 0.50 | 2 | 0 [b] | 3 | 11 |

[a] Yields are determined by VPC, and are based on the amount of trioxane used.
[b] The volumes of the reaction mixtures were equal.

1—3), apparently due to decreased formation of polymeric by-products. Increase of the catalyst concentration resulted in an increased reaction rate, but prolonged exposure to the catalyst caused some destruction of the product (Fig. 2). The presence of an inert solvent such as chloroform was found to be essential since only a small amount of *10* was obtained if the solvent was omitted (runs 4—5).

In analogy with the accepted mechanism for the reaction of anisaldehyde with 2-butanone in a mixture of acetic acid and sulfuric acid,[2] the mechanism of the acid-catalyzed reaction of aldehydes and ketones with formaldehyde in chloroform solution may be assumed to involve enolization of the carbonyl compound followed by electrophilic addition of the conjugate acid of formaldehyde to the double bond of the enol. A reaction path based on this assumption is given in Scheme 1. The formation of the mono- and bis-hydroxymethyl

SCHEME 1



compounds *36* and *37* as reaction intermediates is postulated, although neither *36* nor *37* has been detected in the reaction mixtures. It was found, however, that the corresponding hydroxymethyl derivatives of 2-butanone (*36* and *37*, $R=R'=CH_3$) on treatment with formaldehyde in chloroform solution and in the presence of sulfuric acid were rapidly converted to the 1,3-dioxane *10*. Consequently *36* and *37* may be intermediates but will not accumulate in the reaction mixture.

In the reactions of aldehydes with formaldehyde, 1-alkyl-bicyclo[4.4.0]-3,5,7,9-tetraoxadecanes (*41*, $R'=H$) are obtained in addition to the 1,3-dioxanes (*40*, $R'=H$). Their formation is easily understood as a nucleophilic addition of the hemiformal hydroxyl group in *38* ($R'=H$) to the carbonyl group and cyclization of the resulting diol *39* by formaldehyde. Ketones do not react as easily as aldehydes with hydroxyl compounds to form acetals,[10] which explains why bicyclotetraoxadecanes were not obtained from the ketones investigated. It has been reported by Olsen,[3] however, that cyclohexanone reacts with formaldehyde in a mixture of acetic acid and sulfuric acid to give the bismethylene ether of bis(hydroxymethyl)cyclohexanone hydrate.

The ratio between the yields of 1,3-dioxanes and bicyclotetraoxadecanes obtained from aldehydes (Table 1) increases with the size of the alkyl group of the aldehyde, which is most clearly demonstrated by comparing the product ratios in the reactions of propionaldehyde and isovaleraldehyde with trioxane. Since corresponding 1,3-dioxanes and bicyclotetraoxadecanes were found to be rapidly interconvertible by treatment in refluxing chloroform solution with trioxane-sulfuric acid and sulfuric acid, respectively, it is assumed that the two products are formed under equilibrium conditions. The shift of the equilibrium towards the 1,3-dioxane with increasing size of the alkyl group would then be understood as being due to the increased steric strain caused by this group in the bicyclotetraoxadecane.

The reactions of ketones with formaldehyde under the conditions used gave rise to only small amounts of volatile by-products, as indicated by vapour phase chromatography. These by-products may involve compounds of types *2*—*4*, in which all α-hydrogen atoms have been substituted. In the reaction of 3-pentanone with trioxane (molar ratio 2:1), bis-hydroxymethylation of one of the two methylene groups was favoured, 1,3-dioxane *18* being obtained in a high yield (Table 1). The remaining methylene group in *18* is

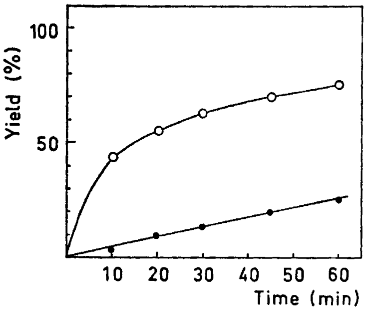


*Fig. 3.* The formation of compounds *18* (○) and *4* (●) from 3-pentanone and *18*, respectively, and trioxane.

considerably less reactive than the methylene groups of 3-pentanone, as was shown by comparative experiments in which 3-pentanone and *18* were treated with trioxane under similar conditions, in the presence of sulfuric acid. The yields of the reaction products, *18* and *4*, respectively, were determined by vapour phase chromatography, and the results are given in Fig. 3. From the initial slopes of the curves, the initial rate of the formation of *18* from 3-pentanone is found to be about twelve times the initial rate of the formation of *4* from *18*. The comparatively low reactivity of the methylene group of *18* and similar 1,3-dioxanes may be due to steric hindrance caused by the 1,3-dioxane ring.

As pointed out before,[7] substitution of 2-butanone and other methyl n-alkyl ketones with formaldehyde under the conditions used takes place in the 3-methylene group rather than in the 1-methyl group. This preference of orientation has previously been found in acid-catalyzed deuteration,[11,12] halogenation,[13] acylation,[14] and aldol reactions,[2,15] and has been suggested to be due to the greater tendency of methyl n-alkyl ketones to form the enol involving the methylene group rather than that involving the methyl group, since hyperconjugative stabilization is more effective in the former enol.[11,13,16] When boron trifluoride etherate was used as a catalyst in the reaction of trioxane with methyl n-alkyl ketones, a by-product with a boiling point slightly higher than that of the main product was obtained in each case. NMR and IR spectra of the by-product obtained in the case of 2-butanone strongly indicated its structure to be 5-propionyl-1,3-dioxane, *i.e.* the 1,3-dioxane formed in the reaction of formaldehyde with the 1-position of 2-butanone. In all cases investigated vapour phase chromatography indicated the yield of the by-product to be about 10 % of that of the main product. However, when the reactions were performed in the presence of sulfuric acid or aluminium chloride as catalyst, only traces of the by-product were formed. It may be noted that in the acid-catalyzed C-acylation of methyl n-alkyl ketones with acid anhydrides the methylene derivatives are obtained exclu-

*Table 4.* Yields of 1- and 3-substituted products in the reactions of 4-substituted methyl ketones with formaldehyde.

$$\overset{1}{CH_3}-\overset{2}{CO}-\overset{3}{CH_2}-R$$

| Catalyst<br>R | $H_2SO_4$ | | BF$_3$-etherate | | $AlCl_3$ | |
|---|---|---|---|---|---|---|
| | 1-subst. | 3-subst. | 1-subst. | 3-subst. | 1-subst. | 3-subst. |
| $CH_3$ | — | 98 | *ca.* 7 | 68 | — | 50 |
| $CH_2CH_3$ | — | 80 | *ca.* 6 | 55 | — | 21 |
| $CH(CH_3)_2$ | 6 | 37 | 33 | 33 | 9 | 12 |
| $C(CH_3)_3$ | 6 | — | 32 | — | 9 | — |

sively if *p*-toluenesulfonic acid is used as a catalyst, whereas the boron trifluoride catalyzed reaction yields a mixture of the two possible isomeric $\beta$-diketones.[14]

As can be seen from Table 1, substitution of the 4-carbon atom in methyl ketones with alkyl groups increases the degree of 1-substitution with formaldehyde; in Table 4 the yields of 1- and 3-substituted products from methyl ketones with an increasing number of methyl groups in the 4-position are collected. The increasing tendency of 1-hydroxymethylation with increasing number of methyl groups in the 4-position may be explained in two ways. The hyperconjugative stabilization of the "3-enol", $CH_3-C(OH)=CH-CR'R''R'''$ ($R=H$ or alkyl), decreases with increasing number of alkyl substituents, and consequently the proportion of 3-enol decreases. The possibility of reaction between formaldehyde and the "1-enol", $CH_2=C(OH)-CH_2-CR'R''R'''$, will increase, thus leading to increased formation of 1-substituted products. Furthermore, as the number of alkyl substituents on the 4-carbon atom increases, the attack of the conjugate acid of formaldehyde on the double bond of the 3-enol will be sterically hindered to an increasing extent (*cf.* Ref. 16), whereas the double bond of the 1-enol is free to add the electrophile. Both effects may cooperate in the orientation of the hydroxymethyl substituents. A similar increase in 1-substitution in methyl ketones containing an increasing number of alkyl substituents at the 4-carbon atom has been observed in acid-catalyzed deuteration,[11] halogenation,[13] and acylation with acid anhydrides.[14]

In the reactions of ethyl alkyl ketones (3-alkanones) with formaldehyde similar orientation effects are found as in the reactions of methyl alkyl ketones. Two isomeric 1,3-dioxanes were obtained from the ethyl n-alkyl ketones investigated, as shown by NMR spectra and vapour phase chromatography (Table 1). The 1,3-dioxanes derived from the ethyl group were found to be favoured by a factor of 3 over those derived from the alkyl group. In the reaction of 5-methyl-3-hexanone only substitution in the ethyl group occurred. As the isomeric enols of the ethyl alkyl ketones should be stabilized to almost the same extent by hyperconjugation, steric factors might affect the course of the substitution.

## EXPERIMENTAL

Samples of trioxane and 3,3-bis(hydroxymethyl)-2-butanone were supplied by Perstorp AB, Perstorp, Sweden. 3-Hydroxymethyl-2-butanone was synthesized according to Landau and Irany.[17] Commercial purum grade chemicals generally were distilled before use. IR spectra were recorded on a Beckman IR-9 spectrophotometer, and NMR spectra on a Varian A-60 instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane (TMS). Vapour phase chromatography (VPC) was performed using a Perkin-Elmer 800 instrument. Melting and boiling points are uncorrected.

### General procedures

*Aldehydes.* A solution of the aldehyde (1.0 mole) and trioxane (1.67 moles; in the case of isovaleraldehyde 1.33 moles) in chloroform (700 ml) was heated to the boiling point, sulfuric acid (9.8 g, 0.1 mole) or boron trifluoride etherate (28.4 g, 0.2 mole) was added and the mixture refluxed for 4 h (if sulfuric acid was used as a catalyst, the reac-

*Table 5.* Analytical data.

| Compound | Formula | Found |  |  | Calculated |  |  | B.p. °C/mm Hg | M.p. °C |
|---|---|---|---|---|---|---|---|---|---|
|  |  | C | H | Cl | C | H | Cl |  |  |
| *5* | $C_6H_{10}O_3$ |  |  |  |  |  |  | 59–60/0.5 |  |
| *6* | $C_7H_{12}O_3$ | 58.30 | 8.37 |  | 58.31 | 8.39 |  | 65–66/0.5 |  |
| *7* | $C_8H_{14}O_3$ |  |  |  |  |  |  | 64–65/0.4 |  |
| *8* | $C_8H_{14}O_3$ |  |  |  |  |  |  | 61–62/0.2 |  |
| *9* | $C_6H_{10}O_3$ | 55.14 | 7.85 |  | 55.37 | 7.75 |  | 39–40/0.3 |  |
| *10* | $C_7H_{12}O_3$ | 58.32 | 8.44 |  | 58.32 | 8.37 |  | 74–76/2.4 |  |
| *11* | $C_8H_{14}O_3$ | 60.67 | 8.92 |  | 60.74 | 8.92 |  | 76–77/2.8 |  |
| *12* | $C_9H_{16}O_3$ | 62.79 | 9.33 |  | 62.77 | 9.36 |  | 88–89/1.7 |  |
| *13* | $C_9H_{16}O_3$ | 62.47 | 9.56 |  | 62.77 | 9.36 |  | 66–67/0.9 |  |
| *14* | $C_9H_{16}O_3$ | 62.64 | 9.61 |  | 62.77 | 9.36 |  | 66–67/0.9 |  |
| *15* | $C_{10}H_{17}O_3Cl$ | 54.47 | 7.96 | 15.75 | 54.42 | 7.77 | 16.07 | 105–130/2.0 |  |
| *16* | $C_{10}H_{18}O_3$ | 64.68 | 9.64 |  | 64.49 | 9.74 |  | 53–55/0.2 |  |
| *17* | $C_{11}H_{19}O_3Cl$ | 56.87 | 8.42 | 15.59 | 56.28 | 8.16 | 15.11 | 107–123/2.2 |  |
| *18* | $C_8H_{14}O_3$ | 60.55 | 8.99 |  | 60.74 | 8.92 |  | 67–68/1.8 |  |
| *19* | $C_9H_{16}O_3$ | 62.83 | 9.17 |  | 62.77 | 9.36 |  | 75/1.0 |  |
| *20* | $C_9H_{16}O_3$ |  |  |  |  |  |  |  |  |
| *21* | $C_{10}H_{18}O_3$ | 64.32 | 9.73 |  | 64.49 | 9.74 |  | 75–77/0.4 |  |
| *22* | $C_{10}H_{18}O_3$ |  |  |  |  |  |  |  |  |
| *23* | $C_{10}H_{18}O_3$ | 64.17 | 9.74 |  | 64.49 | 9.74 |  |  | 53–54 |
| *24* | $C_{11}H_{20}O_3$ | 66.04 | 9.86 |  | 65.97 | 10.07 |  | 96/0.9 |  |
| *25* | $C_{11}H_{20}O_3$ |  |  |  |  |  |  |  |  |
| *26* | $C_{12}H_{22}O_3$ | 66.95 | 10.41 |  | 67.25 | 10.35 |  | 112–113/3.7 |  |
| *27* | $C_{11}H_{12}O_3$ | 68.74 | 6.51 |  | 68.73 | 6.30 |  | 152–155/4.0 | 49–49.5 |
| *28* | $C_{12}H_{14}O_3$ | 70.13 | 7.10 |  | 69.88 | 6.84 |  |  | 90–91 |
| *29* | $C_{12}H_{14}O_3$ | 69.92 | 6.89 |  | 69.88 | 6.84 |  | 117–123/0.6 |  |
| *30* | $C_{17}H_{16}O_3$ | 76.21 | 6.28 |  | 76.10 | 6.01 |  |  | 149–150 |
| *31* | $C_8H_{12}O_3$ | 61.51 | 7.98 |  | 61.52 | 7.75 |  | 70–72/0.8 | 70–71 |
| *32* | $C_7H_{12}O_4$ | 52.40 | 7.52 |  | 52.49 | 7.55 |  | 73–74/0.5 | 45–46 |
| *33* | $C_8H_{14}O_4$ | 55.30 | 8.02 |  | 55.18 | 8.04 |  | 75–76/0.5 | 25–28 |
| *34* | $C_9H_{16}O_4$ |  |  |  |  |  |  | 68–70/0.4 | 23–26 |
| *35* | $C_9H_{16}O_4$ |  |  |  |  |  |  | 65–66/0.2 | 26–29 |

tion mixture was vigorously stirred). Water was removed continuously by a water trap. After cooling to room temperature the reaction mixture was washed with water, neutralized with sodium bicarbonate, and dried over anhydrous calcium sulfate.

*Ketones.* The procedure was similar to that used for the aldehydes. For the majority of the ketones summarized in Table 1 the reaction mixtures were composed as follows: Ketone, 0.25 mole; trioxane, 0.125 mole; chloroform, 50 ml; conc. sulfuric acid, 2 ml, or boron trifluoride etherate, 3.55 g (0.025 mole). The reaction time was 1 h in the case of sulfuric acid, and 2 h in the case of boron trifluoride etherate.

If aluminium chloride was used as a catalyst, 0.083 mole of the latter was added to a stirred solution of the ketone (0.25 mole) and trioxane (0.33 mole) in chloroform (50 ml). After the initial exothermic reaction the mixture was refluxed for 2 h. After cooling to room temperature the mixture was washed with water, neutralized with sodium bicarbonate and dried over calcium sulfate.

Some experiments, in which the composition of the reaction mixture and the reaction time differed from those given above, are described below.

The yields of the reaction products were determined by VPC (Table 1), and the products separated by distillation *in vacuo*, and crystallization. Chromatography on a silica gel column (eluent benzene/ethyl acetate 4:1) was used to separate the isomeric

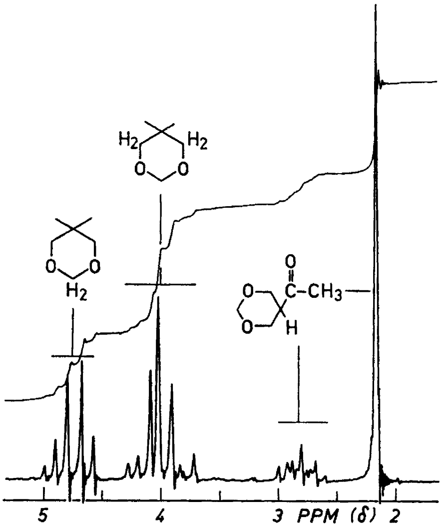


*Fig. 4.* NMR spectrum of 5-acetyl-1,3-dioxane (*9*).

1,3-dioxanes *13* and *14* from the mixture obtained by distillation *in vacuo* of the crude reaction product. The effluent fractions were examined by VPC and thin layer chromatography. Similarly, distillation *in vacuo* followed by silica gel chromatography (eluent benzene/ethyl acetate 4:1) was applied in the purification of the chloromethyl compound *15*.

IR and NMR spectra (for examples, see Figs. 4, 5, and 6) of all products were consistent with the assigned structures. Elemental analysis data as well as b.p. and m.p. of the products are summarized in Table 5. Correct analytical values could not be obtained for compounds *5*, *7*, *8*, *34*, and *35*, due to difficulties in the separation of corresponding 1,3-dioxanes and bicyclotetraoxadecanes. The compounds were, however, characterized by their IR and NMR spectra (*cf.* Figs. 5 and 6).

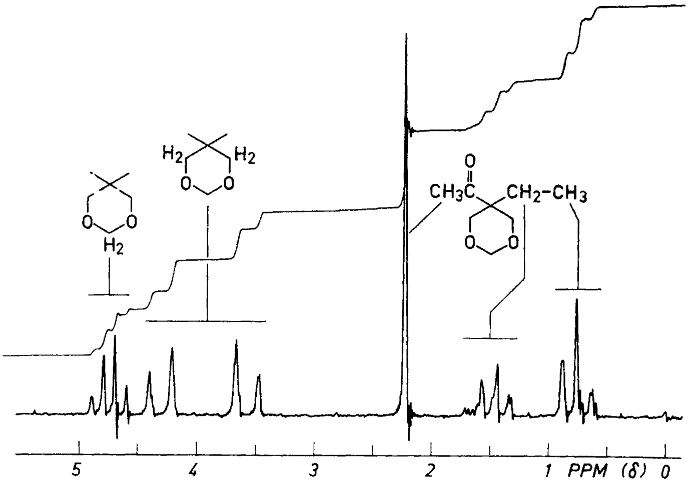


*Fig. 5.* NMR spectrum of 5-acetyl-5-ethyl-1,3-dioxane (*11*).

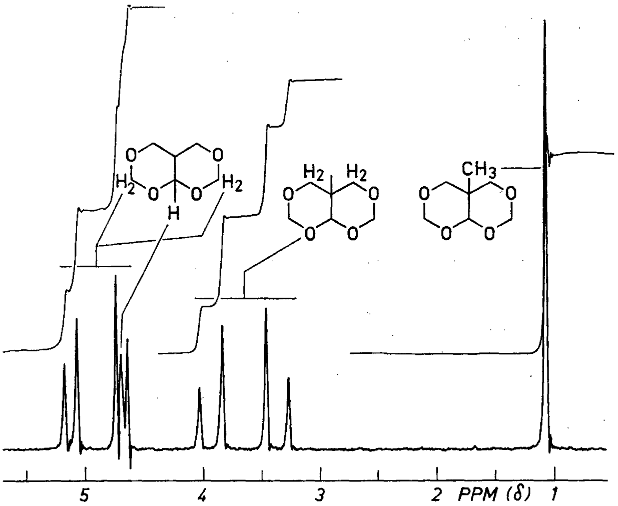


*Fig. 6.* NMR spectrum of 1-methyl-bicyclo[4.4.0]-3,5,7,9-tetraoxadecane (*32*).

From the reaction mixture obtained in the reaction of 2-butanone with trioxane in the presence of boron trifluoride etherate a product with a boiling point slightly higher than that of the main product, 1,3-dioxane *10*, was separated by distillation *in vacuo*. Spectral data indicated its structure to be 5-propionyl-1,3-dioxane. NMR spectrum (*cf.* the spectra of *9* and *11*, Figs. 4 and 5): 4.85 ppm, quartet ($O-CH_2-O$); 4.1 ppm, multiplet ($C-CH_2-O$); 2.9 ppm, multiplet ($>CH-CO-$); 2.55 ppm, quartet ($-CO-CH_2-$); 1.05 ppm, triplet ($-CH_3$). IR spectrum (all strong absorptions): 1710 cm$^{-1}$ ($>C=O$); 1150 cm$^{-1}$, 1030 cm$^{-1}$, and 930 cm$^{-1}$ (1,3-dioxane ring[18]).

*Reaction of 4,4-dimethyl-2-pentanone with trioxane. a) With sulfuric acid.* The reaction was carried out according to the general procedure given for ketones, but the following amounts of the components were used: 4,4-Dimethyl-2-pentanone, 23.5 g (0.21 mole); trioxane, 17.3 g (0.19 mole); chloroform, 100 ml; conc. sulfuric acid, 2.5 ml. After a reaction time of 90 min the mixture was washed with water, neutralized with sodium bicarbonate, and dried over anhydrous calcium sulfate. The solvent was removed under reduced pressure together with unchanged 4,4-dimethyl-2-pentanone (8.1 g), and the residue distilled *in vacuo* through a Vigreux column. The main fraction (b.p.$_{2.2}$ 79–80°) was purified by chromatography on a silica gel column (eluent benzene/ethyl acetate 4:1). The product was characterized as 5-(3,3-dimethylbutyryl)-1,3-dioxane (*16*) by IR and NMR spectra and by elemental analysis. Yield 2.1 g (6 %).

*b) With boron trifluoride etherate.* With 3.5 g (0.025 mole) of the catalyst, 10.9 g (32 %) of compound *16*, b.p.$_{0.2}$ 53–55°, was obtained after a reaction time of 2 h. Chromatographic purification was unnecessary in this case.

*c) With aluminium chloride.* To a stirred solution of 4,4-dimethyl-2-pentanone (22.7 g, 0.20 mole) and trioxane (24 g, 0.27 mole) in chloroform (250 ml) 33.3 g (0.25 mole) of the catalyst was added, and the mixture refluxed for 4 h. After treatment with dilute hydrochloric acid and ice, washing with water and neutralizing with sodium bicarbonate solution, the organic phase was dried over anhydrous sodium sulfate and the solvent as well as unchanged ketone were removed under reduced pressure. The residue was distilled *in vacuo*. The main fraction (b.p.$_{2.2}$ 107–123°) was purified by chromatography on a silica gel column (eluent benzene/ethyl acetate 4:1). Although correct analytical values (Table 5) could not be obtained in spite of repeated distillation and chromatography, the product was characterized as 5-(3,3-dimethylbutyryl)-5-chloromethyl-1,3-dioxane (*17*) by IR and NMR spectra. IR spectrum (all strong absorptions): 1710 cm$^{-1}$ ($>C=O$); 1165 cm$^{-1}$, 1038 cm$^{-1}$, and 930 cm$^{-1}$ (1,3-dioxane ring[18]). NMR spectrum (*cf.* the spectrum of *9*, Fig. 4): 4.79 ppm, quartet ($O-CH_2-O$); 4.01 ppm, singlet ($C-CH_2-O$); 3.87 ppm, singlet ($C-CH_2-Cl$); 2.45 ppm, singlet ($-CO-CH_2-$); 1.05 ppm, singlet ($-CH_3$). Yield 4.4 g (9 %).

*Reaction of 3-hexanone with trioxane.* Conc. sulfuric acid (2.4 ml) was added to a stirred solution of 3-hexanone (40 g, 0.4 mole) and trioxane (32.4 g, 0.36 mole) in chloroform (80 ml), the mixture was refluxed for 90 min with continuous removal of water and worked up according to the general procedure given above. Distillation under reduced pressure gave a main fraction of b.p.$_{1.0}$ 75°, which was shown by elemental analysis, VPC, and NMR spectroscopy to consist of a mixture of two isomeric 1,3-dioxanes, 5-butyryl-5-methyl-1,3-dioxane (*19*) and 5-ethyl-5-propionyl-1,3-dioxane (*20*), in the proportion 72:28. The isomers were not separated. Total yield 36.6 g (59 %).

*Reaction of 3-octanone with trioxane.* The reaction, carried out in the same way as that with 3-hexanone, gave a mixture of isomeric 1,3-dioxanes (b.p.$_{0.9}$ 96°), which was shown by elemental analysis, VPC, and NMR spectroscopy to consist of 5-hexanoyl-5-methyl-1,3-dioxane (*24*) and 5-butyl-5-propionyl-1,3-dioxane (*25*) in the proportion 3:1. The isomers were not separated. Total yield 44.8 g (62 %).

*5-Benzoyl-1,3-dioxane* (27). A mixture of acetophenone (60 g, 0.5 mole), trioxane (60 g, 0.67 mole) and conc. sulfuric acid (5 ml) in chloroform (150 ml) was treated according to the general procedure. Reaction time, 2 h. Unchanged acetophenone (20 g) was distilled off through a Claisen head at 76°/8 mm Hg, and the residue distilled *in vacuo* through a Vigreux column. The main fraction (b.p.$_4$ 152—155°) crystallized on cooling and was identified as 5-benzoyl-1,3-dioxane (*27*) by IR and NMR spectra. M.p. 49.0—49.5° (lit.[9] 49.5—50.0°) after recrystallization from diisopropylether. Yield 18 g (19 %).

*5-Benzoyl-5-methyl-1,3-dioxane* (28). *a*) *With boron trifluoride etherate.* Propiophenone (33.5 g, 0.25 mole) was treated with trioxane (15 g, 0.17 mole) and conc. sulfuric acid (1 ml) in chloroform (40 ml) according to the general procedure. Reaction time, 2 h. After removal of the solvent under reduced pressure the residue (37.8 g) partially crystallized on cooling. The crystals (29 g) were filtered off and recrystallized from chloroform-hexane 1:5 to yield colourless needles, m.p. 90—91°. The compound was characterized as 5-benzoyl-5-methyl-1,3-dioxane (*28*) by IR and NMR spectra, and by elemental analysis. Yield, 84 %.

*b*) *With aluminium chloride.* Aluminium chloride (13.4 g, 0.1 mole) was added to a stirred solution of propiophenone (33.5 g, 0.25 mole) and trioxane (15 g, 0.17 mole) in chloroform (40 ml). The mixture was refluxed for 2.5 h, and was then treated with dilute hydrochloric acid and neutralized with sodium bicarbonate. The organic phase was dried over calcium sulfate and the solvent removed under reduced pressure. From the partly crystalline residue 29 g (84 %) of crystalline *28* was obtained.

*5-Acetyl-5-phenyl-1,3-dioxane* (29). *a*) *With boron trifluoride etherate.* The reaction was carried out according to the general procedure with the following amounts of the components: Benzyl methyl ketone, 20 g (0.15 mole); trioxane, 14.4 g (0.16 mole); chloroform, 40 ml; boron trifluoride etherate, 2.2 g (0.015 mole). Reaction time, 100 min. The reaction mixture was washed with water and neutralized with sodium bicarbonate, dried over anhydrous calcium sulfate, and the solvent removed under reduced pressure. The residue was distilled *in vacuo*. The main fraction (b.p.$_{0.6}$ 117—123°) was characterized as 5-acetyl-5-phenyl-1,3-dioxane (*29*) by IR and NMR spectra and by elemental analysis. Yield 16.6 g (54 %).

*b*) *With aluminium chloride.* Aluminium chloride (10 g, 0.075 mole) was added during 3 min to a stirred solution of benzyl methyl ketone (20 g, 0.15 mole) and trioxane (14.5 g, 0.16 mole) in chloroform (30 ml). An exothermic reaction occurred, and more chloroform (10 ml) was added to the gel-like reaction mixture, which then was refluxed for 45 min. After treatment with dilute hydrochloric acid, water, and sodium bicarbonate, the chloroform solution was dried over sodium sulfate and the solvent removed under reduced pressure. The residue (16.5 g) was distilled *in vacuo*, yielding 6.2 g (20 %) of *29*.

*5-Benzoyl-5-phenyl-1,3-dioxane* (30). Boron trifluoride etherate (2.2 g, 0.015 mole) was added to a solution of benzyl phenyl ketone (29.4 g, 0.15 mole) and trioxane (14.5 g, 0.16 mole) in chloroform (50 ml). The reaction mixture was kept under nitrogen and refluxed for 2 h, water being continuously removed by a water trap. The mixture was washed with water, neutralized with sodium bicarbonate and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the oily residue partially crystallized on cooling, yielding 29 g of crystalline product, which after recrystallization from chloroform-petroleum ether gave colourless prisms, m.p. 149—150°. The product was characterized by IR and NMR spectra and by elemental analysis as 5-benzoyl-5-phenyl-1,3-dioxane (*30*).

*1,3-Dioxane-5-spiro-2′-cyclopentanone* (31). *a*) *With aluminium chloride.* Aluminium chloride (22.5 g, 0.17 mole) was added during 5 min to a stirred solution of cyclopentanone (45 g, 0.53 mole) and trioxane (45 g, 0.5 mole) in chloroform (100 ml). After the initial exothermic reaction the mixture was heated to reflux for 90 min. After the addition of 100 ml chloroform the reaction mixture was worked up according to the general procedure. The solvent was removed under reduced pressure, the oily residue was distilled *in vacuo*, and the main fraction (b.p.$_{0.8}$ 70—72°) obtained crystallized on cooling. Recrystallization from petroleum ether yielded colourless prisms, m.p. 70—71°. The product was characterized as 1,3-dioxane-5-spiro-2′-cyclopentanone (*31*) by IR and NMR spectra and by elemental analysis. Yield 3.6 g (4.5 %).

*b*) *With boron trifluoride etherate.* A solution of cyclopentanone (45 g, 0.53 mole), trioxane (45 g, 0.5 mole), and boron trifluoride etherate (7.6 g, 0.053 mole) in chloroform (200 ml) was treated according to the general procedure. Reaction time, 105 min. The dark red solution was filtered through a 5 cm layer of silica gel in order to remove polymeric material. The solvent was removed under vacuum, and the residue distilled *in vacuo* to yield 7.5 g (10 %) of *31*.

*Reaction of butyraldehyde with trioxane under various conditions.* Solutions of butyraldehyde and trioxane in chloroform were refluxed in the presence of boron trifluoride etherate (see Table 2 and Fig. 1). Water was removed continuously from the solutions by a water trap. Samples were withdrawn 0.5, 1.5, 3.0, 4.0, and 7.0 h after the addition of the catalyst, cooled rapidly to 0° and neutralized with sodium bicarbonate. The yields of the reaction products (*6* and *33*) were determined by VPC. The results obtained are given in Table 2 and Fig. 1.

*Reaction of 2-butanone with trioxane under various conditions.* Vigorously stirred solutions of 2-butanone and trioxane in chloroform were refluxed in the presence of sulfuric acid (see Table 3 and Fig. 2). Water was removed continuously by a water trap. Samples were withdrawn 0.5, 1.0, 1.5, 2.0, and 3.0 h after the addition of the catalyst, cooled rapidly to 0° and neutralized with sodium bicarbonate. The yield of 5-acetyl-5-methyl-1,3-dioxane (*10*) was determined by VPC. The results obtained are given in Table 3 and Fig. 2.

*Reaction of 3-hydroxymethyl-2-butanone* (36, $R=R'=CH_3$) *with trioxane.* A solution of 3-hydroxymethyl-2-butanone (8.0 g, 0.078 mole) in chloroform (25 ml) was added during 6 min to a vigorously stirred refluxing solution of trioxane (9.6 g, 0.11 mole) in chloroform (75 ml), containing sulfuric acid (2 ml). Water was removed continuously by a water trap. After an additional 14 min the solution was cooled to room temperature and neutralized with sodium bicarbonate. The yield of *10* was found to be 8.5 g (75 %) by VPC.

*Reaction of 3,3-bis(hydroxymethyl)-2-butanone* (37, $R=R'=CH_3$) *with trioxane.* A vigorously stirred solution of 3,3-bis(hydroxymethyl)-2-butanone (13.2 g, 0.1 mole) and trioxane (5.0 g, 0.056 mole) in chloroform (100 ml) was heated to reflux. Concentrated sulfuric acid (2 ml) was added. Water was continuously removed by a water trap. After a reaction time of 20 min the mixture was cooled to room temperature and neutralized with sodium bicarbonate. The yield of *10* was found to be 13.3 g (94 %) by VPC.

*Reaction of 5-ethyl-5-formyl-1,3-dioxane* (6) *with trioxane.* A stirred solution of *6* (28.8 g, 0.20 mole) and trioxane (6.0 g, 0.067 mole) in chloroform (140 ml) was heated to reflux and sulfuric acid (1.5 g) was added. Samples were withdrawn 1.0, 3.5, and 5.0 h after the addition of the catalyst, cooled rapidly to 0° and neutralized with sodium bicarbonate. The yield of the reaction product (*33*) and the amount of unchanged *6* were determined by VPC. Equilibrium between the two compounds, 45 % of *6* and 55 % of *33*, was reached within 1 h.

*Treatment of 1-ethyl-bicyclo*[*4.4.0*]*-3,5,7,9-tetraoxadecane* (33) *with sulfuric acid.* A stirred solution of *33* (34.8 g, 0.20 mole) in chloroform (140 ml) was heated to reflux. Sulfuric acid (1.5 g) was added, and samples were withdrawn 1.0, 2.0, and 3.0 h after the addition of the catalyst. The samples were cooled rapidly to 0° and neutralized with sodium bicarbonate. The yield of the reaction product (*6*) and the amount of unchanged *33* were determined by VPC. The same equilibrium as in the preceding experiment was reached within 1 h.

*Formation of 5-methyl-5-propionyl-1,3-dioxane* (18) *from 3-pentanone.* Concentrated sulfuric acid (2 ml) was added to a stirred refluxing solution of 3-pentanone (17.2 g, 0.20 mole) and trioxane (9.0 g, 0.10 mole) in chloroform (100 ml). Water was removed continuously by a water trap. Samples were withdrawn 10, 20, 30, 45, and 60 min after the addition of the catalyst. The samples were neutralized with sodium bicarbonate, and the yield of *18* was determined by VPC. The results are presented in Fig. 3.

*Formation of bis(1-methyl-3,5-dioxacyclohexyl) ketone* (4) *from* 18. An experiment similar to the preceding one was carried out with ketone *18*. The yields of the reaction product (*4*) were determined by VPC. An authentic sample of *4* was prepared according to Ref. 6. The results are also given in Fig. 3.

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