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# Preparation of 2-Acetyl-1,3-diketones from Acid Anhydrides and Isopropenyl Acetate

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Anhydrides (or chlorides) of carboxylic acids on reaction with isopropenyl acetate and aluminium chloride give 2-acetyl-1,3-diketones in moderate yields. The reaction is fairly general and acyclic 2-acetyl-1,3-diketones as well as those with five-, six-, and even seven-membered rings have been prepared.

The preparation of the following compounds is described: 2-acetylcyclopentane-1,3-dione, 2-acetyl-4-methylcyclopentane-1,3-dione, 2-acetyl-4,4-dimethylcyclopentane-1,3-dione, 2-acetylindane-1,3-dione, 2-acetyl-5,5-dimethylcyclohexane-1,3-dione, 2-acetylcycloheptane-1,3-dione and triacetylmethane.

By-products, side reactions and the mechanism of the reaction are discussed.

We have recently reported the preparation of 2-acetylcyclopentane-1,3-dione * and 2-acetylcyclohexane-1,3-dione by diacylation of isopropenyl acetate with anhydrides of succinic and glutaric anhydrides, respectively,[1] as well as the analogous preparation of 2-acetylcyclopent-4-ene-1,3-diones from maleic anhydrides.[2]

The present paper deals with the application of the diacylation method to anhydrides of some substituted succinic and glutaric acids. It also illustrates the use of adipic, phthalic and acetic anhydrides for the preparation of 2-acetylcycloheptane-1,3-dione, 2-acetylindane-1,3-dione and triacetylmethane, respectively. Examples on the use of acid chlorides are also given.

The favoured procedure is addition of isopropenyl acetate to a stirred mixture of the anhydride and aluminium chloride in 1,2-dichloroethane or a similar solvent. The reactions are strongly exothermic and are usually completed by boiling.

The yields now reported are moderate. The reaction seems, however, to be useful for the preparation of cyclic 2-acetyl-1,3-diketones with five-, six-, and even seven-membered rings as well as for the preparation of acyclic ones.[3] The reaction broadens the hitherto limited use of the readily available isopropenyl acetate.[4] It also adds interest to the reactions of other 1-substituted vinyl esters.[5]

* Very recently another synthesis of 2-acetylcyclopentane-1,3-diones has been developed by M. Vandevalle; *Bull. Soc. Chim. Belges.* **73** (1964) 628.

2-Acyl-1,3-diketones are generally sensitive to acids and give β-diketones on standing or heating with dilute acids. The products of acidic cleavage are sometimes important by-products. This cleavage provides a route to β-diketones which are not otherwise readily accessible, *e.g.* cyclopentane-1,3-dione and adipylacetone.

A limitation of the method is imposed by the fact that "tertiary anhydrides" (and "tertiary acyl halides") easily eliminate carbon monoxide on treatment with Lewis acids.[6] For α,α-disubstituted acids this elimination may be a competing reaction and was found to be practically dominant for α,α-dimethylglutaric anhydride. For α,α-dimethylsuccinic anhydride less decarbonylation occurred and 2-acetyl-4,4-dimethylcyclopentane-1,3-dione could be obtained.

Diacylation is here mainly exemplified by anhydrides. However, it is to be understood that it can also be carried out with acid chlorides, as shown by the use of succinyl chloride, phthaloyl chloride and adipoyl chloride.

The mechanism of the diacylation reaction cannot be discussed in detail, but some general aspects may be given. Presumably the reaction involves at least two stages. The first step should be the mono-acylation of isopropenyl acetate by the anhydride to give the enol acetate of a β-diketone. Simultaneously a carboxylate anion (equivalent) is released. The second stage would involve removal of the *O*-acetyl group and a second *C*-acylation. This reaction may proceed *via* a (mixed) anhydride between the carboxyl group released in the first stage and acetic acid (from the *O*-acetyl group). A possible path for the reaction is indicated in Fig. 1. In diacylation by acid chlorides there is

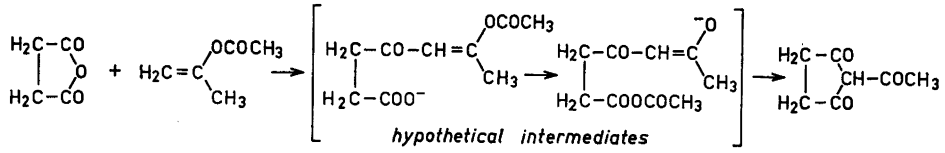


*Fig. 1.* Simplified scheme for the diacylation of isopropenyl acetate in the presence of aluminium chloride. For convenience aluminium complexes and enolisation are not indicated.

no necessity for "acetyl transfers" during the reaction; acetyl chloride is evolved instead. It should be noted that amounts of aluminium chloride greater than two molecules per mole anhydride lead to lower yields. This is presumably due to rearrangement of isopropenyl acetate to acetylacetone caused by the excess of catalyst.

The present reactions of isopropenyl acetate are similar to the reaction between acid chlorides and vinyl acetate described by Sieglitz and Horn.[7] The latter reaction, however, involves the elimination of carbon monoxide from intermediary diacylacetaldehydes to give principally β-diketones. The vinyl acetate reaction did not seem to be well applicable for preparation of cyclic β-diketones.[7]

The first step of the reactions is presumably an electrophilic substitution on the terminal methylene group in isopropenyl acetate. Monoacylation of enol esters by anhydrides in the presence of boron trifluoride has been studied

by Hauser *et al.*[8] For enol acetates this reaction gives boron(fluoride) complexes of β-diketones and is accompanied by the evolution of the volatile and comparatively inert acetyl fluoride. Recently monoacylation of enol ethers has also been described.[9] These reactions are reminiscent of the uncatalysed acylation of enamines.[10]

In the reactions of maleic anhydrides with isopropenyl acetate monoacylation products were observed.[2] In the present series adipylacetone and acetylacetone were obtained from the reactions of adipic and acetic anhydrides, respectively. These products, however, are also readily formed by acidic cleavage of 2-acetylcycloheptane-1,3-dione and triacetylmethane, respectively, and may be secondary products rather than "intermediates".

There are analogies between the present reactions and the acid-catalysed acylation of ketones.[11] Acid-catalysed diacylations of ketones do not seem to be reported. Experiments with acetone, succinyl chloride and aluminium chloride gave no enolic products and the self-condensation of acetone seemed to predominate.

The infrared spectra of the 2-acetylcyclopentane-1,3-diones show three bands in the carbonyl region. This characteristic feature, as well as enolisation, tautomerism and hydrogen bonding is discussed in a separate paper, where NMR data are given in some detail.[12]

## EXPERIMENTAL

Melting points were determined on a micro hot stage. Light petroleum refers to the fraction with b.p. 40–60°. Infrared spectra were recorded for *ca.* 0.1 M solutions in 0.1 mm cells or in potassium bromide discs on a Perkin Elmer No. 21 instrument. Ultraviolet spectra were recorded with a Beckman DK 2 spectrophotometer and NMR spectra on a Varian A 60 spectrometer. Reaction mixtures were screened by chromatography on paper impregnated with dimethyl sulphoxide with ether, light petroleum or isopropyl ether as mobile phase, the spots being detected with iron(III) chloride.

*General procedure for diacylation.* The acid anhydride or chloride (0.1 mole) and anhydrous aluminium chloride (0.2 mole) are suspended in 1,2-dichloroethane (100 ml). Dichloromethane or 1,1,2,2-tetrachloroethane may sometimes be useful alternatives. Isopropenyl acetate (0.1 mole) is added with stirring (if necessary with external cooling). The mixture is boiled (15 min to 2 h) with stirring. The cooled reaction mixture is poured into a mixture of hydrochloric acid (250 ml, 2 M) and crushed ice (250 g). The organic phase is separated and washed with dilute hydrochloric acid. The aqueous phases are extracted with ether (or chloroform), if necessary continuously overnight. The 2-acyl-1,3-diketones may be extracted from the organic phase with sodium hydrogen carbonate (or sodium carbonate) solution and then recovered on acidification. Further purification is achieved *via* copper complexes and distillation or sublimation.

*2-Acetylcyclopentane-1,3-dione.* Details for the preparation from succinic anhydride have been given.[1] Acylation of isopropenyl acetate with succinyl chloride, with addition at 0° and 2 h heating to 50° gives a 45 % yield of 2-acetylcyclopentane-1,3-dione. Due to the hydrophilicity of 2-acetylcyclopentane-1,3-dione continuous extraction is necessary for good yields. The reaction between succinic anhydride and isopropenyl acetate was also conducted with titanium tetrachloride as catalyst. The yield of 2-acetylcyclopentane-1,3-dione was *ca.* 10 %.

*Cyclopentane-1,3-dione.* The acidic cleavage of 2-acetylcyclopentane-1,3-dione must be carried out in dilute solution lest ill-defined oily products should form. 2-Acetylcyclopentane-1,3-dione (0.5 g) is dissolved in hydrochloric acid (50 ml, 2 M) and the solution is heated on a water bath for 12 h. The solvent is distilled off at reduced pressure, the last traces of water being removed azeotropically with benzene. The residue is sublimed at 130° and 0.1 mm. The somewhat oily sublimate (0.28 g) is recrystallised from ethyl acetate to give prisms, m.p. 148–150° (0.22 g, 63 %). Resublimation gives the pure

product, m.p. 152—154°. The infrared spectrum (potassium bromide) is identical with that reported and indicates that the solid is completely enolised; *cf.* Refs.[1,13] Cyclopentane-1,3-dione is somewhat soluble in stabilised chloroform. The infrared spectrum of the solution indicates extensive enolisation but also shows that some diketo form is present. However, if the chloroform is carefully freed from ethanol and dried the solubility drops strongly and the enolisation is suppressed.

*2-Acetyl-4-methylcyclopentane-1,3-dione.* The reaction of α-methylsuccinic anhydride was run in dichloroethane with boiling for 0.5 h. The product was isolated by distillation (b.p. 52°/0.1 mm) in 10 % yield and was purified *via* the copper salt, m.p. 240° (loses solvent at *ca.* 108°). The pure triketone melts at *ca.* 18—19°. (Found C 62.5; H 6.6. Calc. for $C_8H_{10}O_3$: C 62.3; H 6.5). Infrared bands in the carbonyl region (carbon tetrachloride): 1720, 1630, and 1590 $cm^{-1}$. Ultraviolet absorption maxima (cyclohexane): 2650 Å ($\varepsilon = 7800$) and 2205 Å ($\varepsilon = 12\,650$).

*2-Acetyl-4,4-dimethylcyclopentane-1,3-dione.* The reaction of α,α-dimethylsuccinic anhydride was run in dichloroethane with boiling for 2 h. There was some effervescence indicating evolution of carbon monoxide at the beginning of the reaction. The triketone was isolated by distillation and *via* the copper complex, which was recrystallised from methanol, m.p. 224°. The pure product was obtained as an oil, b.p. 52°/0.4 mm in *ca.* 10 % yield. It yellowed on standing. (Found: C 64.2; H 7.3. Calc. for $C_9H_{12}O_3$: C 64.3; H 7.2). Infrared carbonyl bands (carbon tetrachloride): 1700, 1630 and 1585 $cm^{-1}$. Ultraviolet maxima (cyclohexane) 2650 Å ($\varepsilon = 7390$) and 2195 Å ($\varepsilon = 16\,950$).

*2-Acetylindane-1,3-dione.* The reaction with phthalic anhydride was run in 1,1,2,2-tetrachloroethane, the reaction mixture being kept at 80° for 2 h. After decomposition with hydrochloric acid the organic phase was separated and steam distilled. 2-Acetylindane-1,3-dione was isolated from the distillate in 25 % yield by alkali extraction, m.p. 111—113° (lit.[7] m.p. 110—112°). The presence of some indane-1,3-dione (*ca.* 4 %) in the steam distillation residue was noted.

An experiment with phthaloyl chloride in dichloroethane gave *ca.* 10 % yield of 2-acetylindane-1,3-dione.

For comparison it may be noted that Sieglitz and Horn obtained 4 % 2-acetylindane-1,3-dione and 13 % of indane-1,3-dione from vinyl acetate and phthaloyl chloride.[7]

*2-Acetyl-5,5-dimethylcyclohexane-1,3-dione.* The reaction was run with 0.05 mole of β,β-dimethylglutaric anhydride in dichloromethane with boiling for 2 h. The product was isolated by distillation and was purified *via* the copper salt. The pure product was obtained in 10 % yield, m.p. 34—36°. The product was identical with that prepared by *C*-acetylation of dimedone; *cf.* Refs.[14,15]

*2-Acetylcycloheptane-1,3-dione.* Reaction with the polymeric anhydride of adipic acid[16] in dichloroethane. The temperature rose to *ca.* 70°, and the reaction mixture was worked up after cooling. The triketone was isolated by extraction with sodium carbonate solution. Distillation gave the triketone, b.p. 76°/0.3 mm, in 12 % yield. After sublimation it melted at 27—28°. (Found: C 64.4; H 7.2. Calc. for $C_9H_{12}O_3$: C 64.2; H 7.2). Infrared carbonyl absorptions (carbon tetrachloride): 1670 and 1550 $cm^{-1}$. Ultraviolet maxima (cyclohexane): 2800 Å ($\varepsilon = 9730$) and 2360 Å ($\varepsilon = 8340$). The NMR spectrum (*cf.* Ref.[12]) of a carbon tetrachloride solution shows signals for an acetyl group ($\tau = 7.67$) and an enolic proton ($\tau = -7.87$). Two signal groups near $\tau = 7.4$ and 8.15 are assigned to the four methylene groups. The pattern is simplified on addition of triethylamine. Due to rapid proton exchange, it is then reminiscent of an $A_2B_2$ spectrum, as the methylene groups become pairwise equivalent.

2-Acetylcycloheptane-1,3-dione forms a blue copper complex, m.p. 233—234° (from methanol). When this complex is decomposed with dilute acid some "adipylacetone" is invariably formed (see below).

Reaction of adipoyl chloride with isopropenyl acetate in dichloroethane with boiling for 0.5 h gave 17 % 2-acetylcycloheptane-1,3-dione.

*5,7-Dioxononanoic acid (adipylacetone).* 2-Acetylcycloheptane-1,3-dione is sensitive to acids. Thus heating of 0.10 g triketone in 20 ml 0.5 M hydrochloric acid overnight on a water bath gave complete hydrolysis. Extraction with ether afforded a crude product which was recrystallised from light petroleum to give a compound m.p. 41—44° (0.06 g). (Found C 58.1; H 7.6. Calc. for $C_9H_{14}O_4$: C 58.1; H 7.6). The infrared spectrum (potassium bromide) showed the presence of a carboxyl group and an enolised β-diketo system. The NMR spectrum (carbon tetrachloride) showed the presence of an acetyl group ($\tau = 8.00$),

an "olefinic hydrogen" ($\tau = 4.57$) and four methylene groups, two of which should be adjacent to carbonyl groups (signal groups centered at $\tau = 7.7$ and 8.3). Signals from the enolic proton and the carboxylic proton were not seen, presumably due to intermolecular exchange. These facts, as well as the red-violet colour produced with iron(III) chloride, indicate that the compound is the completely enolised 5,7-dioxononanic acid ("adipylacetone") No evidence for the formation of cycloheptane-1,3-dione [17] in the hydrolysis has so far been obtained.

*Triacetylmethane.* The reaction was run with acetic anhydride in dichloroethane with boiling for 0.5 h. Isolation by continuous extraction with ether, extraction with sodium hydrogen carbonate, continuous ether extraction of the acidified solution and distillation. Triacetylmethane, b.p. 100°/20 mm, was obtained in 10 % yield. IR and NMR spectra were identical with those previously reported for triacetylmethane prepared by acetylation of acetylacetone.[15,18]

From other fractions acetylacetone (*ca.* 25 %) and a small amount of 2,6-dimethylpyrone (*ca.* 0.5 %) were isolated. The first may have been formed by hydrolysis of triacetylmethane, rearrangement of isopropenyl acetate or by mono-acylation.

*Unsuccessful attempts.* α,α-Dimethylglutaric acid rapidly evolves carbon monoxide on contact with aluminium chloride. An attempt to add equivalent amounts of the anhydride and isopropenyl acetate to a cold, stirred suspension of aluminium chloride in dichloroethane gave extensive CO elimination and the main product was the lactone of 4-hydroxyisovaleric acid (*ca.* 60 %, identified by b.p. 98–99°/20 mm and by IR and NMR spectra). Only traces of enolic material were obtained.

Reaction of tetrahydrophthalic anhydride (from maleic anhydride and butadiene) in dichloroethane with boiling 1 h gave a product which was isolated *via* sodium carbonate extraction and distillation (*ca.* 8 g, 40 %). Infrared spectra and colour reactions were very similar to those of 2-acetyl-3a,4,7,7a-tetrahydroindane-1,3-dione [2] (obtained from 2-acetylcyclopent-4-ene-1,3-dione and butadiene [2]). The oil did not crystallise even on seeding and presumably there had been partial rearrangement of the double bond under the vigorous reaction conditions.

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