

Preparation of 2-Acetylcyclopent-4-ene-1,3-diones from Maleic Anhydrides and Isopropenyl Acetate

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2-Acetylcyclopent-4-ene-1,3-diones (parent compound, 4-methyl-, 4-chloro-, and 4,5-dimethyl derivatives) have been prepared in *ca.* 10 % yields from maleic anhydrides and isopropenyl acetate in 1,2-dichloroethane or 1,1,2,2-tetrachloroethane in the presence of aluminum chloride. The reactions are complex, and fumarylacetones as well as enol lactones have been observed.

4-Acetylcyclopent-4-ene-1,3-dione reacts with butadiene to give 2-acetyl-3a,4,7,7a-tetrahydroindane-1,3-dione. It can be hydrogenated to 2-acetylcyclopentane-1,3-dione and further to 2-ethylcyclopentane-1,3-dione.

Recent results on the reaction between isopropenyl acetate and anhydrides of succinic and glutaric acids have indicated a general method for the preparation of β -tricarboxyl compounds which seems to be particularly useful for otherwise inaccessible cyclopentane derivatives.^{1,2}

The present communication deals with the application of this method to the preparation of 2-acetylcyclopent-4-ene-1,3-diones using maleic anhydrides. Known compounds of this type include the natural product calythrone (2-isovaleryl-4,5-dimethylcyclopent-4-ene-1,3-dione), which has been prepared from dimethyl dimethylmaleate and 4-methylpentan-2-one with sodium hydride,³ as well as a dehydration product of humulinic acid⁴ and the naturally occurring linderone (2-cinnamoyl-4,5-dimethoxycyclopent-4-ene-1,3-dione).⁵

Isopropenyl acetate reacts readily with maleic anhydride in the presence of aluminum chloride. Reactions were run in dichloromethane, 1,2-dichloroethane, and 1,1,2,2-tetrachloroethane. At low temperatures fumarylacetone was a main product. Reaction at 50 to 100° for short periods of time produced 2-acetylcyclopent-4-ene-1,3-dione (1) in *ca.* 5 % yield together with fumarylacetone (2) and 4-acetylidenebut-2-en-4-olide (4). Acetylcyclopentenedione was isolated by alkali extraction followed by formation of the copper complex. Prolonged heating of the reaction mixture led to complicated mixtures of high-melting products.

The reactions of methylmaleic anhydride and chloromaleic anhydride with isopropenyl acetate were run in 1,2-dichloroethane. Paper chromatography of samples taken after the first vigorous reaction indicated that small amounts of the desired products had been formed but that the bulk of the

enolic material consisted of non-cyclised enolic products. However, when the reaction mixtures were boiled for several hours, ring closure was effected and 2-acetyl-4-methylcyclopent-4-ene-1,3-dione and 2-acetyl-4-chlorocyclopent-4-ene-1,3-dione could be isolated in yields of *ca.* 10 %. Neutral products were also observed in these cases, which from infrared spectra seemed to be enol lactones. They were not further investigated.

The reaction with dimethylmaleic anhydride required drastic conditions; prolonged boiling in 1,1,2,2-tetrachloroethane gave 2-acetyl-4,5-dimethylcyclopent-4-ene-1,3-dione in *ca.* 10 % yield.

The yields in the present reactions are only on the order of 10 % in contrast to yields on the order of 50 % for 2-acetylcyclopentane-1,3-dione.¹

The detailed mechanism of the reaction is not clear, but some possible intermediates are indicated in Fig. 1. The reaction apparently proceeds stepwise. After the mono-acylation step, *cis-trans* isomerisation can give fumarylacetone derivatives (2), although this reaction is probably reversible. The intermediary maleylacetone (3) derivative may either cyclise to enol lactones like 4-acetylidenebut-2-en-4-olide (4) or to 2-acetylcyclopent-4-ene-1,3-diones (1). However, due to the strain in the highly unsaturated ring the latter do not appear to be favoured. Mono-acylation has so far not been observed in the corresponding reactions of succinic and glutaric anhydrides with isopropenyl acetate, although mono-acylation of enol esters with boron trifluoride and acid anhydrides is well known.⁶

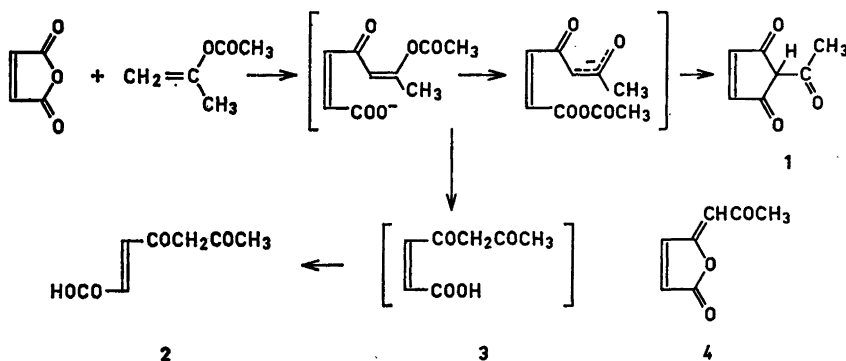


Fig. 1. Simplified scheme for the reaction of maleic anhydride and isopropenyl acetate. The intermediates (in brackets) are as yet hypothetical.

In their exploration of the reaction between acid chlorides and vinyl acetate, Sieglitz and Horn⁷ tried to react "maleinyl chloride" vinyl acetate, but without success. Otherwise, "maleinyl chloride" has apparently not been used in Friedel-Crafts condensations. Maleic anhydride has been frequently employed for the preparation of β -aroylacrylic acids.⁸

Calythron is reported to be stable towards strong acids,⁹ and the same seems to be true for the acetylcyclopentenediones prepared in the present study. This contrasts with the acid lability of most other β -tricarboxyl compounds, and implies that acetylcyclopentenediones, once formed, should

be stable to acids after the reaction. In this respect, they contrast with 2-acetylcyclopentane-1,3-dione,¹ for example.

The 4-acetylcyclopent-4-ene-1,3-diones are pale yellow compounds which dissolve in alkali to give deep yellow solutions. The ultraviolet spectra contain two strong bands that are strongly affected by substitution, and a weak band at *ca.* 3200 Å, which is responsible for the colour. The infrared spectra, with three strong bands in the 1700–1500 cm⁻¹ region, show similarities to those of calythrone and linderone. The spectra show that the acetylcyclopentenediones are completely enolised in solution and in the solid state. This contrasts with the fact that cyclopent-4-ene-1,3-dione is completely ketonic.¹⁰

2-Acetylcyclopent-4-ene-1,3-dione and the 4,5-dimethyl derivative have sharp melting points. However, 2-acetyl-4-methyl- and 2-acetyl-4-chlorocyclopent-4-ene-1,3-dione have broad melting point intervals and seem to occur in two slowly interconvertible forms. This is analogous to the behaviour of other β-tricarbonyl compounds which are completely enolised but can occur in more than one enolic form.¹¹ In the present case, four enols are possible (Fig. 2, 5a–5d). Hydrogen bonding and enolisation in the acetylcyclopentenediones will be discussed in a forthcoming paper.¹²

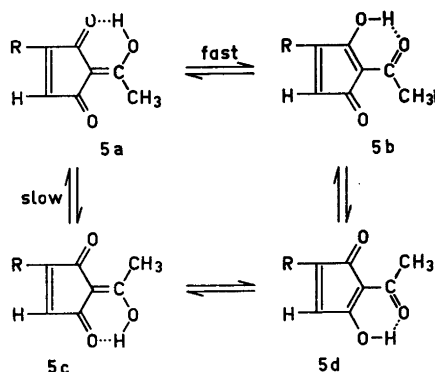


Fig. 2. Enol-enol equilibria for an unsymmetrical 2-acetylcyclopent-4-ene-1,3-dione.

In analogy with cyclopent-4-ene-1,3-dione, the 4-acetyl compound reacts with butadiene to give an adduct which is evidently 2-acetyl-3a,4,7,7a-tetrahydroindane-1,3-dione. Catalytic hydrogenation gives 2-acetylcyclopentane-1,2-dione, which in turn is rapidly reduced to 2-ethylcyclopentane-1,3-dione. The preferential reduction of the carbonyl group in the side chain is analogous to findings for five-ring hop constituents.¹³

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 on *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 instrument and NMR spectra on a Varian A60 spectrometer. Chromatograms were run dimethyl sulphoxide-impregnated paper with ether as mobile phase¹⁴ and were sprayed with iron (III) chloride in methanol.

Maleic anhydride and isopropenyl acetate. Isopropenyl acetate (0.1 mole) was added with stirring to a suspension of finely powdered maleic anhydride (0.1 mole) and anhyd-

rous aluminum chloride (30 g) in 1,1,2,2-tetrachloroethane over a period of 10 min. The reaction started immediately bringing the temperature to *ca.* 100°. The colour changed *via* yellow to dark red. The mixture was left to cool and was then poured with stirring into dilute hydrochloric acid (250 ml, 2 M) containing some ice. The organic phase was separated and the aqueous layer extracted with dichloromethane. The combined organic phases were washed with dilute hydrochloric acid and with water and then extracted with sodium hydroxide (2 × 50 ml, 2 M). The deep yellow extract was acidified and extracted with ether. The washed and dried ether extract was evaporated and the volatile part was sublimed at 100°/10 mm. The sublimate (1.1 g) was dissolved in a small volume of methanol and an excess of copper (II) acetate in water added. A light green copper salt separated. It was filtered off and suspended in hot methanol. After cooling, the copper complex, now dark green, was collected and washed with methanol (0.91 g, decomposes above 270°). It was shaken with ether and dilute sulphuric acid. Evaporation of the washed and dried ether solution gave 4-acetylcyclopent-4-ene-1,3-dione as a pale yellow solid, m.p. 83–84°, in 5 % yield (0.71 g). Recrystallisation from light petroleum and sublimation did not improve the m.p. (Found: C 60.9; H 4.9. Calc. for C₇H₆O₃: C 60.9; H 4.4). The carbonyl part of the infrared spectrum (chloroform solution) contained bands at: 1700 (s), 1630 (vs) and 1595 cm⁻¹ (vs). Ultraviolet maxima (cyclohexane): 2230 Å ($\epsilon=14\ 000$), 2590 Å ($\epsilon=13\ 800$) and 3170 Å ($\epsilon=820$). 2-Acetylcyclopent-4-ene-1,3-dione gave a brownish red colour with iron(III) chloride.

The neutral fraction from the organic phase was sublimed (100°/10 mm) to give a solid, m.p. 60–90° (0.4 g). Recrystallisation from cyclohexane and sublimation gave pale yellow prisms, m.p. 97–101°. (Found: C 61.5; H 4.5; O 34.3. Calc. for C₇H₆O₃: C 60.9; H 4.4; O 34.8). This isomer of acetylcyclopentenedione could be 4-acetonylidenebut-2-en-4-olide. The carbonyl region of the infrared spectrum (KBr) showed bands at: 1785, 1770, 1685, 1620, and 1555 cm⁻¹; the high-frequency bands indicate enol lactone structures. Ultraviolet maximum (cyclohexane): 2900 Å ($\epsilon=11\ 500$). It is possible that a lower-melting product was also present in the neutral fraction.

The NMR spectrum (chloroform-*d* solution) showed the presence of (1) one methyl group, $\tau=7.64$ and three signal groups in the olefinic region; (2) $\tau=3.72$, (3) $\tau=3.52$, and (4) $\tau=1.70$. Signals 3 and 4 gave an AX-type spectrum, J_{34} 5.6 c/s. In addition there were long-range couplings: J_{24} *ca.* 1.8 c/s and K_{23} *ca.* 0.6 c/s. Signals 3 and 4 are obviously due to protons at a *cis*-double bond and signal 2 to the lone "acetonylidene" proton.

The original water phase was continuously extracted with ether overnight. The ether solution was evaporated to give a yellow solid (*ca.* 8 g) which was extracted with several portions of boiling benzene. On cooling, these extracts deposited almost colourless needles (*ca.* 1 g). The product was recrystallised from benzene (or water) and was sublimed (120°/0.1 mm) to give colourless needles, m.p. 158–160°. The compound was titrated as a dibasic acid against thymolphthalein, and was found to have an equivalent weight of 76.3; thus the molecular weight is 153. The equivalent weight and the analysis are consistent with 4,6-dioxohept-2-enoic acid. (Found: C 53.2; 5.1. Calc. for C₇H₆O₄: C 53.8; H 5.2; *M* = 156). Ultraviolet absorption (ethanol): λ_{\max} 3120 Å ($\epsilon=3120$), 2400 Å ($\epsilon=5090$) and *ca.* 2120 Å (ϵ *ca.* 6400). In cyclohexane the bands were found at 3150, 2410, and 2120 Å, and in 1 M HCl at 3130 Å ($\epsilon=9900$), 2500 Å ($\epsilon=5400$), *ca.* 2130 Å ($\epsilon=5300$). Infrared absorption (KBr): 3000–2000 cm⁻¹ (carboxylic type), 1700 (vs) (COOH), 1650 (s) (double bond?), 1600 (vs, broad) (enolised diketone).

Maleyl- and fumarylacetonone have been obtained in connection with the biological degradation of homogentisic acid^{15,16} but have not been completely characterized. However, it is reported that fumarylacetoacetic acid¹⁶ melts at 157–159°, close to the value observed for the present dioxoheptenoic acid. It is also reported that the fumarylacetoacetic acid is slowly decarboxylated even at room temperature. The ultraviolet absorption of maleyl- and fumarylacetonone at 3150 Å has been reported,¹⁵ the present value agreeing in magnitude with that given for fumarylacetonone (0.1 M HCl, $\epsilon=13\ 500$).

The NMR spectrum was recorded for solutions in dimethyl sulphoxide with and without added triethylamine. It showed the presence of (1) one methyl group, $\tau=7.79$, (2) one olefinic proton at $\tau=3.9$ (in pure dimethyl sulphoxide two separate signals were seen at 3.9 and 3.7, which collapsed upon the addition of triethylamine), apparently due to the proton at carbon atom 5 in the enolic form. Two additional olefinic protons gave an AB-type spectrum, (3) $\tau=3.3$ and (4) $\tau=3.1$, with the coupling constant $J_{34}=$

15.5 c/s. In addition a broad signal due to the two acidic protons was observed at $\tau=1.5$. The spectrum is consistent with 4,6-dioxohept-2-enoic acid and the large coupling constant for the neighbouring olefinic protons indicates a *trans*-configuration. The acid is thus *fumarylacetone*.

Some fumarylacetone could also be obtained from the non-volatile part of the acidic fraction from the organic phases.

Prolonged heating of the reaction mixture or higher temperatures led to lower yields and the formation of complex mixtures of high-melting materials. At lower temperatures, the yield of acetylcyclopentenedione decreased, but that of fumarylacetone was improved. Evaporation of solutions containing acetylcyclopentenedione must be done with some care due to the marked volatility of this compound; it sublimes appreciably even at room temperature.

2-Acetyl-4-methylcyclopent-4-ene-1,3-dione. Isopropenyl acetate (0.1 mole) was added with stirring to a mixture of methylmaleic anhydride (0.1 mole) and anhydrous aluminum chloride (30 g) in 1,2-dichloroethane (100 ml). A vigorous reaction started which brought the mixture to a boil towards the end of the addition. A sample was taken, decomposed with dilute hydrochloric acid, and chromatographed on paper. There were fairly large amounts of a slow enolic component and small amounts of a rapid component. From analogy with paper chromatograms of acetylcyclopentenedione and fumarylacetone, the slow component could be a methylfumarylacetone and the rapid one acetylmethylcyclopentenedione. After 2 h reflux, the rapid component dominated. The mixture was left to cool and was then poured into dilute hydrochloric acid (250 ml, 2 M) containing ice (250 g). The organic phase was separated and the aqueous phase was extracted with chloroform. The combined organic phases were washed and dried, the solvents removed and the residue distilled to give a yellow oil, b.p. 75–80°/10 mm (*ca.* 6 g). The infrared spectrum indicated the presence of both acetylmethylcyclopentenedione and enol lactone. The oil was dissolved in some methanol, and copper(II) acetate in water was added. The green precipitate was filtered off, washed with methanol, and then shaken with ether and sulphuric acid. Evaporation of the ether extract gave a yellow oil, which solidified on standing (1.8 g, 12 % yield). Recrystallisation from light petroleum and sublimation gave 2-acetyl-4-methylcyclopent-4-ene-1,3-dione, m.p. 45–50° (unsharp due to the presence of two interconvertible enolic forms.) (Found: C 63.2; H 5.4. Calc. for $C_8H_8O_3$: C 63.2; H 5.3).

Infrared peaks in the carbonyl region (chloroform): 1715 (s), 1660 (vs), 1630 (vs), and 1620 cm^{-1} (shoulder). Ultraviolet maxima (cyclohexane): 2310 Å ($\epsilon=17\ 900$), 2610 Å ($\epsilon=15\ 300$), and 3200 Å (ϵ *ca.* 670).

2-Acetyl-4-chlorocyclopent-4-ene-1,3-dione. Reaction of chloromaleic anhydride and isopropenyl acetate as described above for methylmaleic anhydride gave 2-acetyl-4-chlorocyclopent-4-ene-1,3-dione in 10 % yield. Sublimation and recrystallisation from light petroleum invariably gave mixtures of two crystalline forms which probably represent two different enolic forms, m.p. *ca.* 75–80° and 85–87°. (Found: C 48.9; H 3.0; Cl 20.9. Calc. for $C_7H_5ClO_3$: C 48.7; H 2.9; Cl 20.5).

Infrared peaks in the carbonyl region (chloroform): 1715 (s), 1660 (vs), 1615 (vs), 1600 (m) and 1565 (s) cm^{-1} . Ultraviolet maxima (cyclohexane): 2450 Å ($\epsilon=21\ 200$), 2650 Å (shoulder, ϵ *ca.* 15 500) and 3200 Å ($\epsilon=520$).

2-Acetyl-4,5-dimethylcyclopent-4-ene-1,3-dione. Isopropenyl acetate (0.05 mole) was added to a stirred suspension of dimethylmaleic anhydride (0.05 mole) and aluminum chloride (15 g) in 1,1,2,2-tetrachloroethane (50 ml). The mixture became hot, but paper chromatograms indicated that only negligible amounts of the desired product had been formed. The mixture was refluxed for 3 h (or more). The cooled reaction mixture was poured into hydrochloric acid (125 ml, 2 M) containing some ice. Ether was added, the mixture was thoroughly shaken, and then filtered through celite. The organic phase was separated and the aqueous phase extracted with ether. The combined organic phases were extracted with sodium hydrogen carbonate (saturated) and sodium hydroxide (2 M) solutions. The hydrogen carbonate extract after acidification and re-extraction gave a crystalline material (3.4 g) which was sublimed at 100°/10 mm. The sublimate was dissolved in methanol and treated with aqueous copper(II) acetate to give a copper complex (1.03 g, m.p. 277–279° decomp.) The copper complex, after washing with methanol, was decomposed with sulphuric acid to give 2-acetyl-4,5-dimethylcyclopent-4-ene-1,3-dione (0.93 g, 11 %) which was purified by recrystallisation from light

petroleum and sublimation, m.p. 51–52°. (Found: C 65.0; H 6.0. Calc. for $C_7H_{10}O_2$: C 65.1; H 6.1).

Infrared peaks (carbon tetrachloride): 1720 (s), 1660 (vs), 1630 (vs), and 1620 cm^{-1} (shoulder). Ultraviolet maxima (cyclohexane): 2380 Å ($\epsilon=23\ 200$), 2620 Å ($\epsilon=18\ 100$), and 3100 Å (ϵ ca. 600).

The sodium hydroxide fraction contained largely dimethylmaleic anhydride. This was also obtained from the non-complex-forming part of the hydrogen carbonate fraction (total ca. 3 g). The neutral fraction contained material with infrared absorption at 1770 cm^{-1} , presumably enol lactones.

Diene adduct. A solution of 4-acetylcyclopent-4-ene-1,3-dione in benzene was saturated with butadiene and left in a stoppered flask for four days. The solvent was removed. The crystalline residue (m.p. 41–45°) was sublimed in a gradient tube (100°/0.1 mm) and was recrystallised from a small volume of light petroleum to give colourless prisms, m.p. 48–50°, obviously 2-acetyl-3a,4,7,7a-tetrahydroindane-1,3-dione. (Found: C 68.9; H 6.1. Calc. for $C_{11}H_{14}O_2$: C 68.7; H 6.3).

Infrared peaks (chloroform): 1700 (s), 1630 (vs), and 1590 cm^{-1} (vs). The ultraviolet absorption was similar to that of 2-acetylcyclopentane-1,3-dione¹: 2210 Å ($\epsilon=10\ 800$) and 2650 Å ($\epsilon=8000$).

Hydrogenation. 2-Acetylcyclopent-4-ene-1,3-dione (1 mmole) was hydrogenated over palladised charcoal (60 mg, 10 %) in absolute ethanol (10 ml). The hydrogen consumption was steady, and when 1 mmole of hydrogen had been absorbed (2 h), the reaction was interrupted, the catalyst filtered off and the solvent evaporated. The crystalline residue had a broad m.p. range and paper chromatography indicated the presence of 2-acetylcyclopentane-1,3-dione and an additional, slow enolic material. The mixture was dissolved in hot benzene and left to cool. A crystalline solid separated and was filtered off (35 mg, m.p. 168–172°). The mother liquors were evaporated and the residue extracted with boiling light petroleum. The extract was evaporated to a small volume and cooled in a refrigerator. The crystalline material was filtered off and sublimed to give pure 2-acetylcyclopentane-1,3-dione (57 mg), m.p. and mixed m.p. 72–74°.

The high-melting product was recrystallised from benzene and sublimed to give colourless prisms, which changed to plates at ca. 140° and melted at 173–175°. (Found: C 66.7; H 8.0. Calc. for $C_7H_{10}O_2$: C 66.6; H 8.0).

The infrared spectrum (KBr) was similar to that of cyclopentane-1,3-dione.¹⁷ Ultraviolet maxima: in 1 M HCl at 2520 Å ($\epsilon=17\ 600$) and in 1 M NaOH at 2680 Å ($\epsilon=27\ 500$). These values are also similar to those for cyclopentane-1,3-dione. The compound obviously is 2-ethylcyclopentane-1,3-dione.

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