# Acylation of Pyran-2,4,6-trione (Acetonedicarboxylic Anhydride)

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The reaction of acetone-1,3-dicarboxylic acid with acetic anhydride at 40—50 °C gives 4-acetoxypyran-2,6(3*H*)-dione. This *O*-acetyl derivative can be converted into the *C*-acetyl derivative, 3-acetylpyran-2,4,6-trione. Pyran-2,4,6-trione reacts with benzoyl chloride to yield the *O*-benzoyl derivative, 4-benzoyloxypyran-2,6(3*H*)-dione, whereas the reaction with ethoxycarbonylacetyl chloride gives the bis-*C*-acyl derivative, 3,5-bis(ethoxycarbonylacetyl)pyran-2,4,6-trione.

THE reaction of acetonedicarboxylic acid (2-oxoglutaric acid) (1) with acetic anhydride has been reported to yield pyran-2,4,6-trione (2) [1,2] and its monoacetyl (3a—d)[2-4] or diacetyl (4) [2,5] derivatives depending on the reaction conditions. The structures of (2) and (4), which are formed at or below room temperature [1,2] and at elevated temperature with acid catalysis,[2,5] respectively, are well established. The monoacetyl derivative (3) is formed without acid catalysis at a slightly elevated temperature (40—50 °C).[2-4] Malachowski [3] formulated the product as the 4-acetoxy-derivative (3a), whereas Kato and Konno,[4] on the basis of spectroscopic evidence, preferred the tautomeric structure (3b). Later

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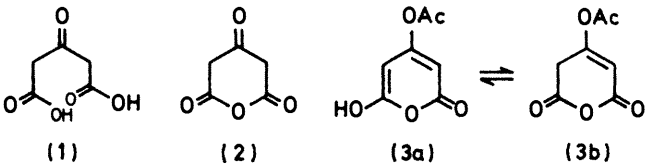
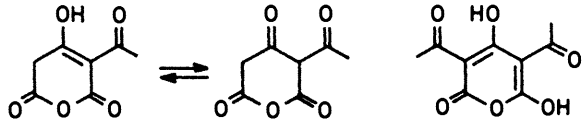
[5] H. von Pechmann and F. Neger, *Annalen*, 1893, **273**, 186; T. Kato and Y. Kubota, *Chem. Pharm. Bull.* (*Japan*), 1966, **14**, 931; C. R. Willis, G.P. 2,544,130; L. W. Chakrin, K. M. Snader, and C. R. Willis, G.P. 2,544,131.

Kiang *et al.*[2] rejected the *O*-acetyl structure [(3a)⇄(3b)] and assigned the *C*-acetyl structure [(3c)⇄(3d)] to the product.* These authors,[2] however, did not comment on the evidence presented by Kato and Konno,[4] nor did they mention the formation of (3c, d) from (3a, b) reported by Malachowski.[3]

In connection with the synthesis of polyketide compounds[7] and higher homologues[8] of 1,6,6aλ⁴-trithiapentalenes we considered the anhydride (2) and the *C*-acetyl derivative (3c, d) to be potentially valuable synthetic precursors. We have therefore studied the



(1) (2) (3a) (3b)



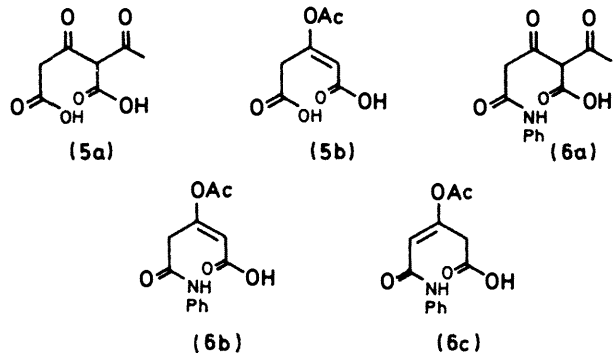
(3c) (3d) (4)

reaction of the acid (1) with acetic anhydride and some related reactions.

## RESULTS AND DISCUSSION

The reaction of acetonedicarboxylic acid (1) with acetic anhydride (following the procedure in ref. 2) gave a product with the reported m.p. and i.r. spectrum.[2] The $^1$H n.m.r. spectrum in $CDCl_3$ was identical with that reported in ref. 4 and supports the *O*-acetyl structure (3b). The spectrum in $(CD_3)_2CO$ was very similar and showed no indication of a tautomeric equilibrium as reported in ref. 2.

Kiang *et al.*[2] also presented some chemical evidence in support of the *C*-acetyl structure (3c, d). They obtained a diacid [(5a), m.p. 106—108 °C] by careful hydrolysis under neutral conditions and a monoanilide [(6a), m.p. 127—128 °C] by reaction with aniline. We repeated these experiments and likewise isolated a diacid (m.p. 108—109 °C) and a monoanilide (m.p. 122—123 °C). The i.r. spectrum of the diacid showed absorptions at 1 780 (enol acetate), 1 720 (saturated carboxylic acid), and 1 700 cm$^{-1}$ (αβ-unsaturated carboxylic acid). The $^1$H n.m.r. spectrum [$(CD_3)_2CO$] showed singlets at δ 1.97 (3 H, $CH_3CO$), 3.73 (2 H, $CH_2$), 5.72 (1 H, CH), and 9.8 (br, 2 H, $CO_2H$). On the basis of these observations we assign the *O*-acetyl structure (5b) to the diacid.† Similarly, the spectroscopic properties (see Experimental section) of the monoanilide are in accord with the *O*-acetyl structure (6b) or (6c), but not with the *C*-acetyl (6a). Neither $^1$H nor $^{13}$C n.m.r. spectra distinguish (6b) and (6c), but the absence of an i.r. absorption in the 1 720—1 700 cm$^{-1}$ region (saturated carboxylic acid), as observed in the spectrum of the diacid (5b), makes (6b)



(5a) (5b) (6a)



(6b) (6c)

the more probable structure. Further chemical evidence for the *O*-acetyl structure (3b) was obtained by hydrolysis with 1 equiv. of water in trifluoroacetic acid; the enol acetate function was hydrolysed selectively to give the anhydride (2) in good yield.

When the *O*-acetyl derivative (3b) was treated with pyridine (in chloroform) the pyridinium salt (7) resulted.[3] The *C*-acetyl derivative (3c, d) was obtained from (7) by reaction with sulphuric acid [65% yield based on (3b)]. In the i.r. spectrum (chloroform) absorptions at 1 800 (anhydride), 1 750 (anhydride), and 1 600 cm$^{-1}$ (enolized β-diketone) were observed. The $^1$H n.m.r. spectrum in $CDCl_3$ ‡ showed singlets at δ 2.70 (3 H, $CH_3CO$), 3.78 (2 H, $CH_2$), and 13.7 (br, 1 H, OH). These observations strongly indicate that the tautomeric form (3c) is predominant in a non-polar solvent. The

$^{13}$C Chemical shifts (p.p.m. from $Me_4Si$) of the products (3c), (7), and (8)

| Carbon atoms | (3c) [a] | (3c) [b] | (7) [b] | (8) [b] |
|---|---|---|---|---|
| Me | 27.03 | 28.40 | 28.72 | 28.78 |
| $CH_2$ | 38.40 | | | |
| Enol-β | 101.23 | 78.10, 93.22 | 78.16, 92.20 | 78.16, 92.20 |
| Other alkene and carbonyl | 158.67, 160.81, 189.79, 202.78 | 164.00, 164.32, 178.22, 197.97 | 163.67, 164.25, 177.44, 197.58 | 163.73, 164.25, 177.51, 197.65 |
| Others | | | 127.22,[c] 142.16,[c] 146.38 [c] | 123.06,[d] 128.13,[d] 129.82,[d] 131.83 [d] |

[a] In $CDCl_3$. [b] In $(CD_3)_2SO$. [c] Pyridinium carbon atoms. [d] Anilinium carbon atoms.

$^{13}$C chemical shifts (Table) support this assignment. In [$^2H_6$]dimethyl sulphoxide the $^{13}$C signal at δ 38.40 ($CH_2$) was replaced by one at 78.10 (see Table). This indicates that further enolization takes place in this

* According to this report the structure was revised in Beilstein's Handbook.[6]

† This explains the absence of enolization, which would be expected with structure (5a).[2]

‡ In acetone the *C*-acetyl derivative (3c) was converted into 5-carboxy-4-hydroxy-6-methyl-3,6-dihydropyran-2-one (see Experimental section).

[6] 'Beilsteins Handbuch der Organischen Chemie,' ed. H.-G. Boit, Springer-Verlag, Heidelberg, 1976, vol. 18, Drittes und Viertes Ergänzungswerk, p. 1142.

[7] T. M. Harris, C. M. Harris, and K. B. Hindley, 'Progress in the Chemistry of Organic Natural Products,' ed. W. Herz, H. Grisebach, and G. W. Kirby, Springer-Verlag, New York, 1974, vol. 31, p. 218.

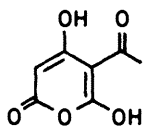
[8] E. G. Frandsen, *J.C.S. Chem. Comm.*, 1977, 851.

solvent [(3e) is one of the possible tautomers]. The $^{13}C$ n.m.r. spectra of (3e) and the pyridinium salt (7) are very similar (Table), indicating that (7) is also doubly enolized.

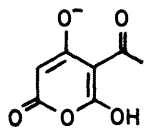
The *C*-acetyl derivative (3c) did not react as reported [2] with water and aniline to give the diacid (5a) and the monoanilide (6a), respectively. When (3c) was treated with water at room temperature evolution of carbon dioxide took place and the oily residue consisted mainly of acetylacetone ($^1H$ n.m.r.). The reaction of (3c) with aniline (in dichloromethane *) gave an anilinium salt (8) with physicochemical properties (see Experimental section and Table) very similar to those of the pyridinium salt (7). On acidification (3c) was recovered.

The conversion of the *O*-acetyl derivative (3b) into the *C*-acetyl derivative (3c) could not be achieved with acidic catalysis. When (3b) was dissolved in trifluoroacetic acid containing a catalytic amount of sulphuric acid in an n.m.r. tube the conversion into an equimolar mixture of the anhydride (2) and the bis-*C*-acetyl derivative (4) was observed. In a preparative experiment equimolar amounts of (3b) and (3c) when heated with sulphuric acid gave (4) in 72% yield. Apparently, the further acetylation of the mono-*C*-acetyl derivative (3c) by the *O*-acetyl derivative (3b) proceeds more easily than the rearrangement (3b) to (3c). The success of the pyridine-catalysed rearrangement (see above) may be due to the insolubility of the pyridinium salt (7) in the reaction medium.

The *O*-acetyl derivative (3b) was also obtained from the anhydride (2) and acetic anhydride. Other acylating reagents, such as benzoyl chloride or ethoxycarbonylacetyl chloride, reacted differently: neither reacted



(3e)



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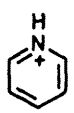
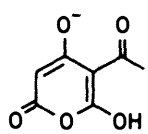
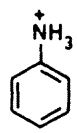
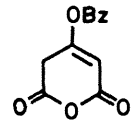


(8)

with (2) at room temperature, and at elevated temperatures complex mixtures resulted. However, the anhydride (2) was easily *O*-benzoylated to (9) with benzoyl chloride in the presence of 1 equiv. of pyridine. Under the same conditions the reaction of (2) with ethoxycarbonylacetyl chloride gave a complex mixture.† However, use of 2 equiv. of ethoxycarbonylacetyl chloride and excess of pyridine gave a pyridinium salt. Acidification of this salt yielded the diacyl derivative [(10) is one of the possible tautomers] in 63% yield. A doubly enolized structure follows from the non-equivalence of two acyl signals in the $^{13}C$ n.m.r. spectrum and the presence of signals from two enol protons (δ 13.5 and 18.6) in the $^1H$ n.m.r. spectrum. This structure also explains the absence of i.r. absorptions (chloroform) in



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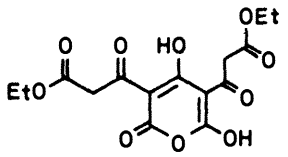

(10)

the 1 850—1 780 $cm^{-1}$ region (anhydride). Thus, the structure of (11) is similar to that of the bis-*C*-acetyl derivative (4).[2,5]

## EXPERIMENTAL

Pyran-2,4,6-trione (2) was prepared from acetone-1,3-dicarboxylic acid (EGA Chemie) by a published procedure.[1] 3,5-Diacetylpyran-2,4,6-trione (4) was prepared by the method of Kiang *et al.*[2] Spectra were recorded on Perkin-Elmer 457 (i.r.), Varian MAT 311A (mass), JEOL PMX-60 ($^1H$ n.m.r.), and JEOL FX-60 instruments ($^{13}C$ n.m.r.).

*4-Acetoxypyran-2,6(3H)-dione* (3b).—Acetone-1,3-dicarboxylic acid (10 g) was added in portions to acetic anhydride (20 g) and the mixture was stirred for 24 h at room temperature. It was then cooled to 10 °C, and the resulting crystals were filtered off and washed with benzene. The combined filtrate and washings were cooled to 0 °C to give a second crop of crystals. The combined crops were recrystallized from benzene to give (3b) (8.8 g, 76%), m.p. 90—92 °C (lit.,[2] 88—89 °C; lit.,[3] 91—92 °C); $\nu_{max.}$ (KBr) 3 105, 3 085, 2 965, 2 915, 1 812, 1 765, 1 735, and 1 665 $cm^{-1}$: $\delta_H(CDCl_3)$ 2.30 (3 H, s), 3.69 (2 H, d, *J* 1.7 Hz), and 6.32 (1 H, t, *J* 1.7 Hz); $\delta_C$ ($CDCl_3$) 21.27, 33.98, 104.54, 159.90, 160.94, 162.50, and 166.40; *m/e* 170 (1%, $M^+$), 84 (9), and 43 (100).

The reaction of the anhydride (2) (14.1 g) with acetic anhydride (24 g) and acetic acid (7 g) similarly gave also the *O*-acetyl product (3b) (15.4 g, 82%).

*3-Acetoxypent-2-enedioic Acid* (5b).—Neutral hydrolysis of 4-acetoxypyran-2,6(3*H*)-dione (3b) (1.26 g) by the method of ref. 2 gave 3-acetoxypent-2-enedioic acid (5b), m.p. 108—109 °C (0.7 g, 51%); for i.r. and $^1H$ n.m.r., see Results and Discussion section; $\delta_C[(CD_3)_2CO]$ 20.92, 37.10, 112.15, 160.16, 166.92, 168.41, and 169.32.

*Monoanilide of 3-Acetoxypent-2-enedioic Acid* (6b *or* c).—4-Acetoxypyran-2,6(3*H*)-dione (3b) (1.0 g) was treated with aniline (0.56 ml) in glacial acetic acid (2 ml) (see ref. 2) to yield the monoanilide of 3-acetoxypent-2-enedioic acid (6b or c), m.p. 122—123 °C (1.1 g, 71%); $\nu_{max.}$ (KBr) 1 756, 1 686, and 1 657 $cm^{-1}$; $\delta_H[(CD_3)_2CO]$ 2.17 (3 H, s), 3.98 (2 H, s), 5.97 (1 H, s), 6.8—7.8 (5 H, m), 8.9 (1 H, br s), and 9.3 (1 H, br s); $\delta_C[(CD_3)_2SO]$ 20.92, 38.98, 112.86, 119.16, 123.32, 128.71, 138.98, 159.25, 165.49, 166.59, and 168.09; *m/e* 263 (20%, $M^+$), 203 (30), 93 (100), and 43 (57).

*Pyran-2,4,6-trione* (2) *from 4-Acetoxypyran-2,6(3H)-dione* (3b).—4-Acetoxypyran-2,6(3*H*)-dione (3b) (0.340 g) was dissolved in water (0.036 g) and trifluoroacetic acid (1 ml)

* In glacial acetic acid [2] no water-insoluble products were obtained.

† The $^1H$ n.m.r. spectrum indicated the presence of *O*-acyl and bis-*C*-acyl anhydride, and unchanged starting material.

and set aside for 20 h. The trifluoroacetic acid was evaporated off and the crystalline residue washed with dichloromethane to give pyran-2,4,6-trione (2) (0.180 g, 70%), which had physicochemical constants identical with those of an authentic sample.[1]

*Pyridinium Salt* (7) *of* 5-*Acetyl*-4,6-*dihydroxypyran*-2-*one*.[3]—To a suspension of 4-acetoxypyran-2,6(3*H*)-dione (3b) in chloroform (15 ml) at 0 °C was slowly added pyridine (3.0 g) in chloroform (2 ml). After stirring at 0 °C for 2 h the precipitated crystals (5.7 g, 64%) were collected, and washed with chloroform and then pentane; m.p. 150—152 °C (ethanol) (lit.,[3] 143 °C); $\delta_H[(CD_3)_2SO]$ 2.40 (3 H, s), 4.50 (1 H, br s), 8.0—9.2 (5 H, m), and 14.2 (2 H, br s); for $\delta_C$ see Table.

5-*Acetyl*-4-*hydroxypyran*-2,6(3H)-*dione* (3c).[3]—To a vigorously stirred suspension of the pyridinium salt (7) (2.5 g) in ether (60 ml) at 0 °C was added a mixture of sulphuric acid (1.25 g) and water (2.25 g). The stirring was continued without cooling for *ca.* 5 min. The ether phase was then decanted and the aqueous phase was further extracted with ether (3 × 60 ml). The combined extracts were dried ($CaCl_2$) and evaporated and the residue was rapidly recrystallized from benzene to give 5-acetyl-4-hydroxypyran-2,6(3*H*)-dione (3c) as white crystals, m.p. 126—128 °C (lit.,[3] 125—126 °C) (1.1 g, 65%); for i.r. and $^1H$ n.m.r. see Results and Discussion section; for $\delta_C$ see Table; *m/e* 170 (8%, $M^+$), 152 (18), 126 (24), 124 (16), 98 (28), 84 (20), 69 (28), and 43 (100).

*Anilinium Salt* (8) *of* 5-*Acetyl*-4,6-*dihydroxypyran*-2-*one*.—Aniline (0.110 g) in dichloromethane (6 ml) was added to 5-acetyl-4-hydroxypyran-2,6(3*H*)-dione (3c) (0.170 g) in dichloromethane (15 ml). The precipitated solid was filtered off and washed with dichloromethane. The *anilinium salt* (8), m.p. 127—128 °C (decomp), was obtained in quantitative yield; $\delta_H[(CD_3)_2SO]$ 2.40 (3 H, s), 4.52 (1 H, br s), 7.5 (5 H, m), and 9.8 (4 H, br s); for $\delta_C$ see Table (Found: C, 59.0; H, 4.70; N, 5.12. $C_{13}H_{13}NO_5$ requires C, 59.5; H, 4.98; N, 5.32%). When the anilinium salt (8) was treated with sulphuric acid in the same way as the pyridinium salt (7) (see above), 5-acetyl-4-hydroxypyran-2,6(3*H*)-dione (3c) was recovered in 85% yield.

3,5-*Diacetyl*-4,6-*dihydroxypyran*-2-*one* (4) *from* (3b) *and* (3c).—4-Acetoxypyran-2,6(3*H*)-dione (3b) (0.100 g), 5-acetyl-4-hydroxypyran-2,6(3*H*)-dione (3c) (0.100 g), and sulphuric acid (0.025 g) were heated together at 100 °C for 8 min. Water was added and the resulting white crystals of 3,5-diacetyl-4,6-dihydroxypyran-2-one (4) were collected [0.090 g, 72% based on (3b)]. This sample was identical with one prepared by another route.[2]

4-*Benzoyloxypyran*-2,6(3H)-*dione* (9).—Pyridine (0.476 g) in dichloromethane (4 ml), followed by benzoyl chloride (0.900 g) in dichloromethane (4 ml), was added to a suspension of pyran-2,4,6-trione (2) (0.768 g) in dichloromethane (10 ml), maintaining the temperature below 5 °C. The mixture was then stirred at room temperature for 1 h. After evaporating off the solvent the residue was extracted with hot benzene. White crystals of the *benzoate* (9) precipitated from the benzene solution on cooling; these were collected and recrystallized from benzene–dichloromethane; yield 0.81 g (62%), m.p. 165—167 °C; $\nu_{max.}$ (KBr) 3 120, 3 090, 2 950, 2 930, 1 810, 1 750, 1 735, and 1 650 $cm^{-1}$; $\delta_H[(CD_3)_2CO]$ 4.10 (2 H, d, *J* 1.6 Hz), 6.50 (1 H, t, *J* 1.6 Hz), and 7.3—8.3 (5 H, m); $\delta_C[(CD_3)_2CO]$ 34.70, 104.74, 128.84, 129.75, 131.05, 135.54, 161.46, 163.09, 163.54, and 164.06; *m/e* 105 (100%) and 77 (44) (Found: C, 62.2; H, 3.55. $C_{12}H_8O_5$ requires C, 62.1; H, 3.45%).

3,5-*Bis*(*ethoxycarbonylacetyl*)-4,6-*dihydroxypyran*-2-*one* (10).—To a suspension of pyran-2,4,6-trione (2) (2.56 g) in dichloromethane (30 ml) was added pyridine (6.40 g) in dichloromethane (20 ml) followed by ethoxycarbonylacetyl chloride (7.00 g) in dichloromethane (20 ml), while the temperature was maintained below 25 °C. After stirring for 20 h at room temperature, the solvent was evaporated off and the residue was washed with ether. The residue was suspended in ether (400 ml) at 0 °C, a solution of sulphuric acid (10 g) and water (10 g) was added; the mixture was then stirred for 5 min at room temperature. The ether phase was decanted and the aqueous phase further extracted with ether (2 × 200 ml). The combined ether extracts were dried ($CaCl_2$) and evaporated. The resulting oil was recrystallized from absolute ethanol to give white crystals of 3,5-bis(ethoxycarbonylacetyl)-4,6-dihydroxypyran-2-one (10) (4.5 g, 63%), m.p. 81—82 °C; $\nu_{max.}$ ($CHCl_3$) 1 735br, 1 664, 1 580, and 1 545 $cm^{-1}$; $\delta_H$-($CDCl_3$) 1.29 (6 H, t, *J* 7.2 Hz), 4.08 (4 H, s), 4.32 (4 H, q, *J* 7.2 Hz), 13.5 (1 H, br s), and 18.6 (1 H, br s); $\delta_C(CDCl_3)$ 13.84, 43.47, 46.33, 61.73, 96.49, 97.91, 156.72, 165.68, 166.33, 168.86, 182.71, 190.37, and 197.84; *m/e* 356 (10%, $M^+$), 310 (40), 264 (100), 251 (35), 223 (50), and 222 (48) (Found: C, 50.6; H, 4.65%; $M^+$, 356.070. $C_{15}H_{16}O_{10}$ requires C, 50.6; H, 4.55%; *M*, 356.074).

5-*Carboxy*-4-*hydroxy*-6-*methylpyran*-2-*one*.—5-Acetyl-4-hydroxypyran-2,6-dione (3c) (0.50 g) was dissolved in acetone (3 ml) or acetone–water (60 : 1; 3 ml) and the solution was stirred for 20 h at room temperature. The acetone was evaporated off and the crystalline *residue* was washed with dichloromethane; yield 0.38 g (76%), m.p. 201—202 °C (ethanol); $\nu_{max.}$ (KBr) 1 725, 1 680, and 1 600 $cm^{-1}$; $\delta_H[(CD_3)_2SO]$ 2.60 (3 H, s), 5.27 (1 H, s), and 9.0 (2 H, br s); *m/e* 170 (37%), 152 (17), 142 (38), 124 (80), and 42 (100) (Found: C, 49.35; H, 3.55. $C_7H_6O_5$ requires C, 49.4; H, 3.55%).

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