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Acid-Promoted Reactions of Butan-2,3-dione

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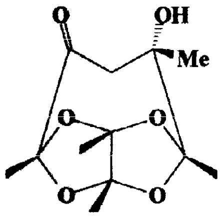
Abstract: Along with the major product (1) by-products of the reaction between butan-2,3-dione and hydrochloric acid were isolated. These include (2), (3), (7) and (9).

Butan-2,3-dione undergoes a variety of dimerisations and trimerisations under basic or acidic conditions.[1-6] This paper describes a set of new dimers and trimers isolated as minor products during the formation of 11-hydroxy-1,3,5,7,11-pentamethyl-2,4,6,9-tetraoxatricyclo[3.3.3.0$^{(3,7)}$]undecan-9-one (**1**) from the reaction between butan-2,3-dione and concentrated hydrochloric acid. Treatment of butan-2,3-dione with concentrated hydrochloric acid at a temperature below 3°C and allowing the mixture to stand at *ca* 10°C for 5 days gave the crystalline trimer **1** in 49.5 % yield. The mother liquor was extracted with diethylether and then with chloroform and the extracts subjected to a variety of chromatographic techniques (see experimental section) to give the minor products.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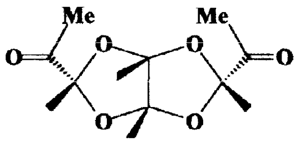

2

The ^{1}H and ^{13}C NMR spectra of the crystalline product mp 80 - 82°C isolated in 2.2% yield are very simple showing three sets of methyl groups and consistent with *endo, endo*-1,5-diacetyl-1,3,5,7-tetramethyl-2,4,6,8-tetraoxatricyclo[3.3.0]octane **2**,[5] the precursor of **1**.

The mass spectrum of the crystalline product mp 88-90°C, isolated in 0.05% yield, indicates the molecular formula $C_{10}H_{14}O_4$ and shows trimerisation followed by loss of a two carbon fragment. The ^{1}H NMR spectrum showed signals for four methyl groups at δ 1.45, 1.47, 2.22 (*J* 0.7 Hz) and 2.23 with signals for a single olefinic proton at δ 5.46 (*J* 0.7 Hz). The presence of an α,β-unsaturated ketone was indicated by IR

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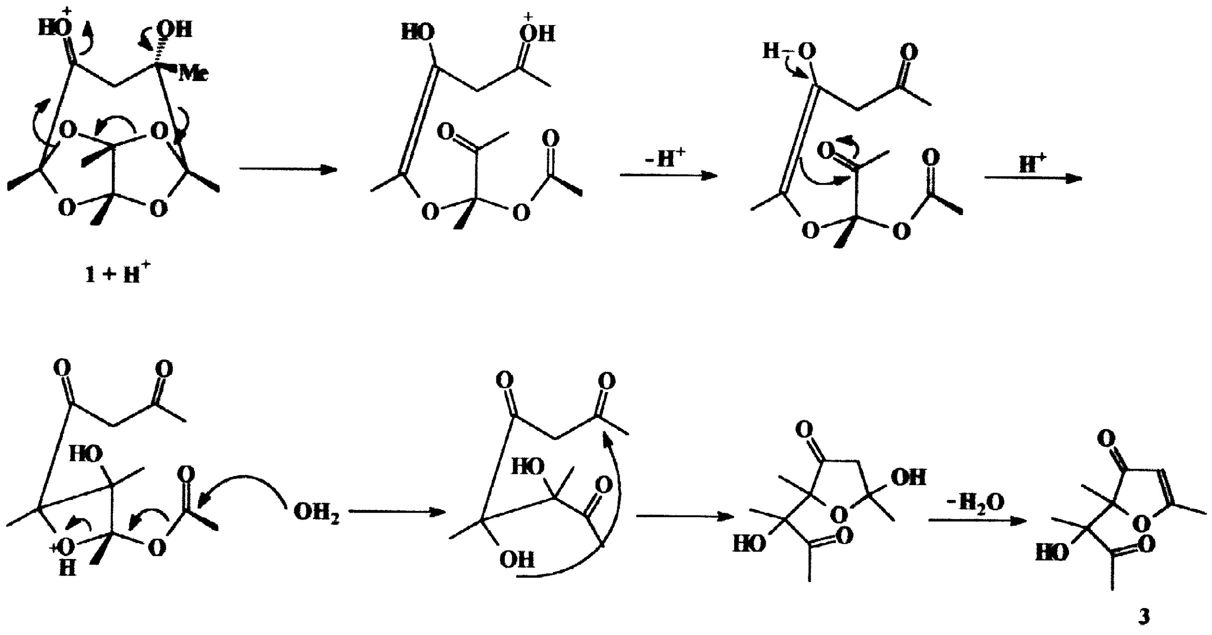
absorption at 1687 cm^{-1}. The spectra are in accord with 2-(1-hydroxy-1-methyl-2-oxopropyl)-2,5-dimethyl-2,3-dihydro-3-furanone **3** and a possible mechanism of formation from protonated **1** is shown in Scheme 1.



Scheme 1 Mechanism for the formation of compound **3**

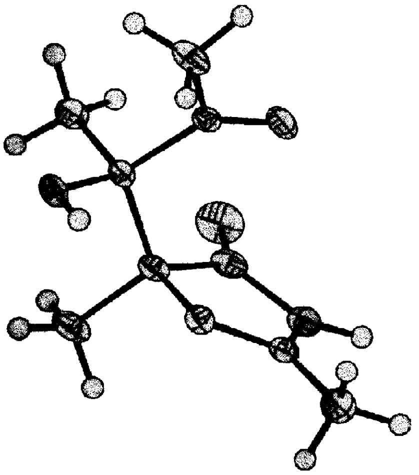
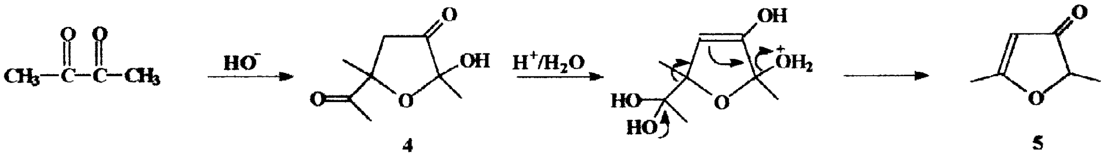


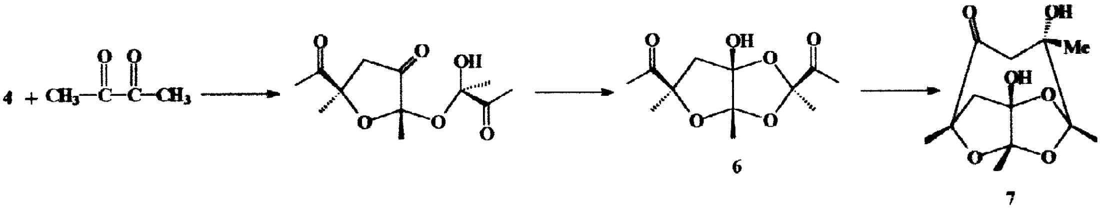
Figure 1 Molecular structure of **3**.

Only one diastereoisomer of **3** was isolated from the reaction mixture and the stereochemistry of this was determined by X-ray analysis[7] (Fig.1). A search was made for the second diastereoisomer *via* the acid catalysed reaction between the furanone **5** and butan-2,3-dione. The furanone was obtained from butan-2,3-dione *via* the dimer **4** according to published methods[8] (Scheme 2). Reaction between the furanone **5** and butan-2,3-dione in the presence of concentrated hydrochloric acid gave crystalline **3** together with an oil containing the diastereoisomer of **3**.



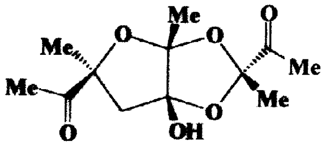
Scheme 2 Preparation of furanone **5** from butan-2,3-dione.

The mass spectrum of the crystalline product mp 190°C, isolated in 0.02% yield gave the formula $C_{12}H_{18}O_6$ indicating another trimer of butan-2,3-dione. The ^1H and ^{13}C NMR spectral data resemble data obtained on the trimer **1** but with the absence of one methyl group, the presence of an additional hydroxyl group and with a second ^1H NMR AB quartet (δ 2.00, 2.84; *J* -12.9 Hz) suggesting 3,11-dihydroxy-1,5,7,11-tetramethyl-4,6,8-trioxatricyclo[3.3.3.0$^{(3,7)}$]undecan-9-one **7**.



Scheme 3 Method for the formation of trimer **7** from the dimer **4**.

Structure **7** rather than that of alternative isomers was supported by heteronuclear and homonuclear COSY and NOESY correlations together with the very probable formation of **7** from the butan-2,3-dione dimer **4** as shown in Scheme 3. It may be noted that **6** is an isomer of the previously isolated **8**.[2]



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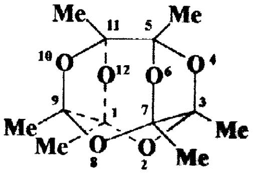


9

A different type of trimeric structure was assigned to the crystalline product $C_{12}H_{18}O_6$ mp 120°C isolated in 0.01% yield. The ^1H NMR spectrum was extremely simple showing only two signals: one at δ 1.46 for two equivalent methyl groups and the second at 1.53 for four equivalent methyl groups. The ^{13}C NMR spectrum showed four signals: two for six methyl carbons at δ 22.1 (2 x CH_3) and at δ 22.5 (4 x CH_3), and two signals for six quaternary carbons at δ 103.8 and 110.2. The spectral data indicates 1,3,5,7,9,11-hexamethyl-2,4,6,8,10,12-hexaoxatetracyclo[5.5.0.0$^{(5.11)}$]dodecane **9** and this was confirmed by X-ray crystallography[7] (Fig.2).

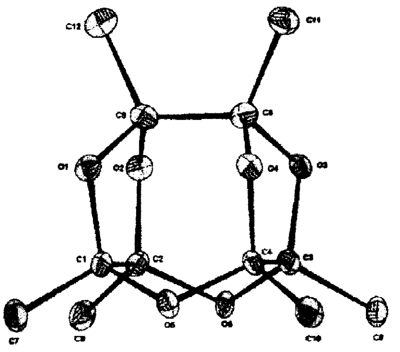
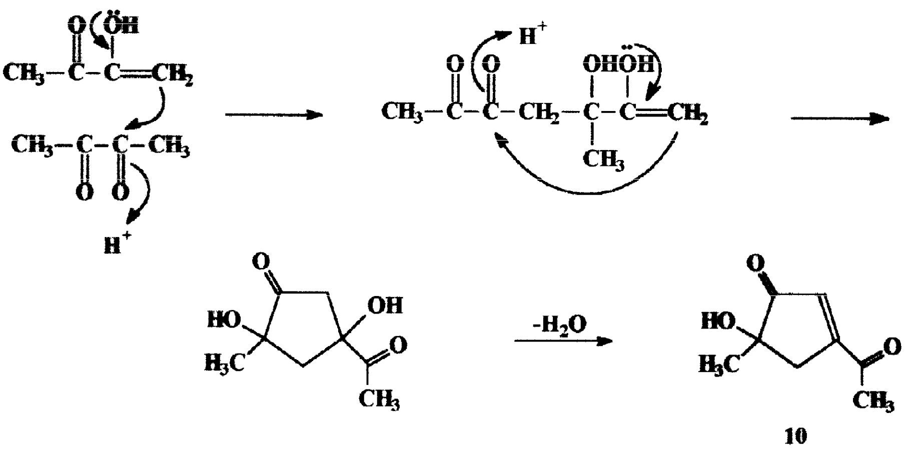


Figure 2 Molecular structure of **9**.

The ^1H NMR spectrum of the minor product (0.007% yield) isolated as an oil showed two methyl signals, one at δ 1.43 (J 0.9 Hz) and the second downfield at δ 2.05 (J 1.5 Hz). In addition there was an AB quartet for a methylene group at δ 2.99 and δ 3.12 (J_{gem} -15.7 Hz, J 0.9 Hz) and a doublet at δ 6.71 (J 1.5 Hz) for a CH proton as well as hydroxyl group proton absorption at δ 3.78. The magnitude of the J_{gem} of the methylene group showed adjacent unsaturation. The ^{13}C NMR spectrum showed absorption for eight different carbon atoms suggesting that the compound is formed from two molecules of butan-2,3-dione. The ^{13}C NMR spectrum showed absorption for eight different carbon atoms suggesting that the compound is formed from two molecules of butan-2,3-dione. The ^{13}C NMR spectrum showed absorption for two methyl carbons (δ 16.2 and 27.6), one methylene carbon (δ 51.9), one methine carbon (δ 134.1) and four quaternary carbons (δ 75.2, 152.1

196.1 and 201.5). The spectral data indicate 3-acetyl-5-hydroxy-5-methyl-cyclopent-2-en-1-one (**10**). A mechanism of formation is shown in Scheme 4.



Scheme 4 Mechanism for the formation of cyclopent-2-en-1-one derivative (**10**).

Experimental

General :

^{1}H and ^{13}C NMR experimental spectra were recorded at room temperature in either deuteriochloroform, deuteriomethanol or deuteriobenzene, at low temperature in deuteriodichloromethane and at high temperature in deuteriopyridine solutions on a JEOL GSX FT spectrometer at 270.16 (^{1}H) and 67.97 (^{13}C) MHz with tetramethylsilane as internal standard. Coupling constants (*J*) are quoted in Hertz. Mass spectra were performed on a JEOL JMS DX 303 mass spectrometer, operating in either an alternating chemical ionisation (CI)-electron impact (EI) low resolution mode or in a high resolution EI mode. Mps were performed on a hot-stage microscope and are uncorrected. IR spectra were recorded on a Perkin Elmer 577 spectrometer.

Thin layer chromatography (TLC) was carried out on glass silica gel (60 G) plates (0.5 mm) with chloroform and 1% of methanol as solvent, unless otherwise specified. Centrifugal TLC was run on a centrifugal TLC, Chromatotron model 7924T with circular silica gel (60 G) plates (4mm) made with 70 G silica and 150 ml water.

Reaction between butan-2,3-dione and hydrochloric acid: Butan-2,3-dione (3 x 250 ml, 3 x 2.85 mol) was placed in three 1l three-necked round bottom flasks cooled in an ice-salt bath (< 3°C). Concentrated hydrochloric acid (3 x 100 ml) was added in small portions over a period of 1.5 h with continuous stirring and the temperature maintained below 3°C. The solutions were initially clear yellow and became gradually more viscous and a milky yellow in colour. The resulting solutions were stirred for a further 4 h and then placed in a refrigerator for 5 days. The crude crystalline product was filtered off and recrystallized from petroleum ether (b.p. 40-60°C), to give 11-hydroxy-1,3,5,7,11-pentamethyl-2,4,6,8-tetraoxatricyclo-[3.3.3.0$^{(3,7)}$]undecan-9-one (**1**) as white crystals m.p. 108-110°C (364.8 g, 49.5%).

The acidic mother liquors from the three reactions were combined together before extracting first with diethyl ether (4 x 200 ml) followed by chloroform (4 x 200 ml). The two organic layers were kept separate but treated in a similar manner: The extracts were washed with distilled water (3 x 150 ml), then with aqueous sodium carbonate solution (2 x 150 ml) and finally the organic layers were dried over anhydrous sodium sulphate. The respective solvents were evaporated *in vacuo* to afford oily residues. The ether extract gave a thick yellow oil (EE) (66.85 g) and the chloroform extract afforded a dark brown oil (CE) (20.1 g). The oil CE was examined by TLC and found to be a mixture of **1** and other unidentified compounds.

Attempts were made to separate the oily mixture by column chromatography using silica gel (300 g, 60 G) eluting with a mixture of petroleum ether (b.p. 40-60°C)/diethyl ether : (60/40). The polarity of this was changed gradually every 500ml (x7) by the addition of 10% diethyl ether. Seventy eluted fractions [CE-(f1 to f70), *ca.* 50ml] were collected and these were examined by TLC. Those that were similar, were combined together giving fourteen different fractions [CE-(f1 to f14)]. Fractional recrystallization of fraction CE-f3 gave **1** (0.382 g, 0.05%). From fractions CE-f4 and CE-f6 respectively compounds **3** and **7** were isolated.

2-(1-Hydroxy-1-methyl-2-oxopropyl)-2,5-dimethyl-2,3-dihydro-3-furanone (**3**) was isolated as white crystals m.p. 88-90°C (0.28 g, 0.05%); ν_{max} (Nujol) 1713, 1687, 3415 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.45 (3 H, s, CH_3), 1.47 (3 H, s, CH_3), 2.22 (3 H, d, *J* 0.7, CH_3), 2.23 (3 H, s, CH_3), 5.45 (1 H, d, *J* 0.7, *CH*), 4.13 (1 H, s, *OH*); δ_C (68 MHz, CDC1$_3$) 208.5 (*C*=O), 189.0 (*C*), 104.3 (*C*H), 91.7 (*C*), 80.8 (*C*), 25.9 (CH_3), 19.1 (CH_3), 17.7 (CH_3), 16.6 (CH_3); HRMS (EI): M$^+$, found 198.0885. $C_{10}H_{14}O_4$ requires 198.0892.

7,11-Dihydroxy-1,5,7,11-tetramethyl-2,4,6-trioxatricyclo[3.3.3.0$^{(3.7)}$]undecan-9-one (**7**) was isolated as white crystals m.p. 190°C (0.15 g, 0.02%); ν_{max} (Nujol) 1697 cm^{-1}; δ_H (270 MHz, CDC1$_3$) 1.26 (3 H, s, CH_3), 1.27 (3, H, s, CH_3), 1.47 (3 H, s, CH_3), 1.57 (3 H, s, CH_3), 1.94 (1 H, d, *J* 10.8, CH_2), 2.00 (1 H, d, *J* 12.9, CH_2), 3.74 (1 H, d, *J* 10.8, CH_2), 2.84 (1 H, d, *J* 12.9, (CH_2), 2.79 (1 H, s, *H*) and 6.74 (1 H, s, *OH*); δ_C (68 MHz, CDC1$_3$) 218.4 (*C*=O), 113.4, 113.3, 110.2, 86.9 (*C*-OH), 80.9(*C*-OH), 51.1 (CH_2), 45.9 (CH_2), 24.3 (CH_3), 21.8 (CH_3), 21.7 (CH_3) and 21.6 (CH_3). HRMS (EI): MH^+, found 259.1177. $C_{12}H_{19}O_6$ requires 259.1182.

The ether extract (EE) was left in the refrigerator (4 weeks) and more crystalline product was deposited. The crystals (30.51 g) were separated from the oily residue (EE1) and fractional recrystallization gave **1** and *endo,endo*-3,7-diacetyl-1,3,5,7-tetramethyl-2,4,6,8-tetraoxatricyclo[3.3.0]octane (**2**) mp 80-82°C (15.93 g, 2.2 %); ν_{max} (Nujol) 1705 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.38 (6 H, s, 2 x CH_3), 1.64 (6 H, s, 2 x CH_3) and 2.23 (6 H, s, 2 x CH_3); δ_C (68 MHz, $CDCl_3$) 205.4 (2 x C=O), 111.7 (2 x C), 108.6 (2 x C), 25.0 (2 x $COCH_3$), 23.8 (2 x CH_3) and 21.9 (2 x CH_3); HRMS (EI): MH^+, found 259.1172. $C_{12}H_{19}O_6$ requires 259.1182.

An attempt was made to separate the compounds in the oily residue (EE1) (34.34 g) by column chromatography using silica gel (400 g, 60G). The mixture was introduced onto the column dissolved in a mixture of petroleum ether (b.p. 40-60°C) and diethyl ether in a ratio of 50/50. Elution was with mixtures of petroleum ether and diethyl ether (5% of diethyl ether changed to 10%, 15% and 20% every 400 ml). Only three fractions [EE-(f1 to f3)] were collected and then the column was left to drain. The first three eluted fractions [EE-(f1 to f3)] contained mainly the same product and fractional recrystallization gave 1,3,5,7,9,11-hexamethyl-2,4,6,8,10,12-hexaoxatetracyclo[5.5.0.0.$0^{(5,11)}$]dodecane (**9**) as white crystals mp 190°C, (0.31 g, 0.04%); ν_{max} (Nujol) 1129, 2985 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.46 (6 H, s, 2 x CH_3) and 1.53 (12 H, s, 4 x CH_3); δ_C (68 MHz, $CDCl_3$) 110.2 (2 x C), 103.8 (4 x C), 22.5 (4 x CH_3) and 22.1 (2 x CH_3). HRMS (EI): M^+, found 258.0996. $C_{12}H_{18}O_6$ requires 258.1104.

The silica column was divided into 11 layers [EE-(L1 to L11)]. Each layer of silica was extracted with chloroform and the solvent evaporated to give oily mixtures [EE-(L1 to L11)] which were examined by TLC. All those giving a similar profiles were combined together to give seven new fractions [EE-(T1 to T7)].

An attempt was made to separate fraction EE-T1 (0.93 g) by centrifugal TLC eluting with mixtures of chloroform and methanol. Thirty fractions ($CHCl_3$, 300 ml), 15 fractions (0.25:99.75, CH_3OH: $CHCl_3$, 300 ml), 10 fractions (0.5:99.5, CH_3OH:$CHCl_3$, 200 ml) and three fractions (100% CH_3OH, 50 ml) were collected. These fractions were examined by TLC and those which were similar were combined to give ten [EE-(f1 to f10)] fractions with different profiles. Fractional recrystallization of fraction EE-f1 gave more 1,3,5,7,9,11-hexamethyl-2,4,6,8,10,12-hexaoxatetracyclo[5.5.0.0.$0^{(5.11)}$]dodecane (**9**) as a single product with m.p. 190°C (0.098 g, 0.013 %) and fraction EE-f3 (0.050 g, 0.007%) gave 3-acetyl-5-hydroxy-5-methyl-cyclopent-2-en-1-one (**10**) as an oil; ν_{max} ($CDCl_3$) 1700 cm^{-1}; δ_H (270 MHz, $CDCl_3$) 1.43 (3 H, d, J 0.9 CH_3), 2.05 (3 H, d, J 1.5 CH_3), 2.99 (2 H, d, J 15.7 and 0.9, CH_2), 3.12 (2 H, d, J 15.7, CH_2), 3.78 (1 H, s, OH) and 6.71 (1 H, d, J 1.5 CH); δ_C (68 MHz, $CDCl_3$) 201.5 (C=O), 196.1 (C=O), 152.1 (C), 75.2 (C), 134.1 (CH), 51.9 (CH_2), 27.6 (CH_3)

and 16.2 (CH_3); HRMS (EI): M^+, found 154.0624. $C_8H_{10}O_3$ requires 154.0630.

Acknowledgement

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