Knoevenagel Reactions with β-Oxo Acids. Regiospecific Enol Equivalents for Syntheses of α,β-Unsaturated Ketones and of Some β-Ketols

David H. Grayson* and Mathew R. J. Tuite
University Chemical Laboratory, Trinity College, Dublin 2, Ireland

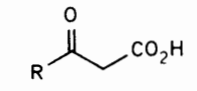
3-Oxobutanoic acid reacts with aliphatic aldehydes in the presence of pyridine to give α,β-unsaturated methyl ketones in good yields. Analogous results were obtained with a series of other β-oxo acids. Synthesis of (*E*)-7-methyloct-4-en-3-one, a major constituent of the marine sponge *Plakortis zygompha*, has been carried out using this methodology. Aromatic aldehydes are generally less reactive under these conditions but give β-ketols when the phenyl ring bears an electron-withdrawing substituent. Some observations on the mechanism of the reaction between 3-oxobutanoic acid and benzaldehyde are presented.

β-Keto esters have been widely utilised as the active methylene component in Knoevenagel reactions,[1,2] but the corresponding β-oxo acids have received relatively little attention in this respect. In 1899, Verley showed[3] that 3-oxobutanoic acid (**1**) condensed with citral in the presence of pyridine to yield pseudoionone. This was followed by Robinson's landmark synthesis of tropinone[4] from 3-oxopentane-1,5-dioic acid, methylamine, and butanedial, which was later refined by Schöpf.[5] Although this synthesis involved Mannich rather than Knoevenagel reactions, it clearly took advantage of the nucleophilic character of the enol form of the β-keto acid. Previously Schöpf[6] had described the reactions of the sodium salts of 3-oxobutanoic acid (**1**) and of 3-oxo-3-phenylpropanoic acid with benzaldehyde and some of its methoxy derivatives. These condensations were performed in neutral phosphate buffers at 25 °C during periods of up to 14 days, and generally gave β-ketols. The reaction of 3-oxobutanoic acid (**1**) with 2-oxopropanal, which gives 3-hydroxyhexane-2,5-dione, has been extensively investigated by Henze,[7,8] Stöhr,[9–11] and Neuburg.[12] Two reports have been published[13,14] on the reaction of 3-oxobutanoic acid (**1**) with glucose, but the product has not been well characterised. However, reaction of the β-oxo acid (**1**) with 2,3-*O*-isopropylidene-D-glyceraldehyde in the presence of pyridine and piperidine has been shown[15] to yield the hexenulose (**2**).

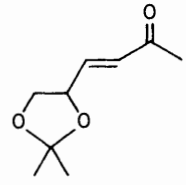
We anticipated that the reaction of β-oxo acids with aldehydes should provide a general synthetic route to α,β-unsaturated ketones. In the present paper, we show that: (i) this expectation can be realised, (ii) explore the scope of the synthesis, and (iii) describe some results obtained with aromatic aldehydes.

The simplest β-oxo acid, 3-oxobutanoic acid (**1**), was first isolated in crystalline form by Kreuger[16] by aqueous alkaline hydrolysis of ethyl 3-oxobutanoate, the free acid being extracted into ether after acidification with sulphuric acid and saturation of the aqueous phase with sodium chloride. The yield obtained when using this method is low (*ca.* 30%). We find that substitution of ammonium sulphate for sodium chloride more than doubles the isolated yield of crystalline β-oxo acid (**1**). This acid can also be synthesized from diketene.[17]

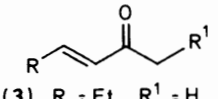
The first α,β-unsaturated ketone whose synthesis was attempted was hex-3-en-2-one (**3**). This is a useful starting material for 3,4-diethylpyrrole,[18] and has previously been prepared by a Wittig synthesis,[19] by the condensation–deacylation of pentane-2,4-dione with propanal[20,21] (only 3% yield in one instance), and by the crossed aldol condensation of propanone with propanal. A number of reports concerning the latter reaction, which proved to be temperamental and unreliable in our hands, have been critically discussed by Dubois.[22] Reaction



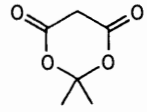
(**1**) R = Me
(**6**) R = Et
(**12**) R = Pr^i
(**15**) R = PhCH$_2$



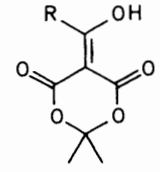
(**2**)



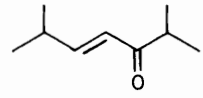
(**3**) R = Et, R^1 = H
(**4**) R = Pr^i, R^1 = H
(**5**) R = Bu, R^1 = H
(**9**) R = Et, R^1 = Me
(**10**) R = Bu^i, R^1 = Me
(**16**) R = Et, R^1 = Ph



(**7**)



(**8**) R = Et
(**11**) R = Pr^i
(**14**) R = PhCH$_2$



(**13**)

of 3-oxobutanoic acid (**1**) and propanal (1 equiv. each) in pyridine solution, gave, after distillation (*E*)-hex-3-en-2-one (**3**) (70%). A number of other solvent–catalyst combinations were examined for this reaction, but neat pyridine regularly gave the best results.

The α,β-unsaturated ketones obtained by treating 3-oxobutanoic acid (**1**) under these conditions with a selection of aliphatic aldehydes are catalogued in Table 1, as are those formed when some other β-oxo acids were used.

3-Oxopentanoic acid (**6**) was prepared by hydrolysis of its methyl ester. This was obtained by acylating 2,2-dimethyl-1,3-dioxane-4,6-dione (**7**) with propanoyl chloride to give compound (**8**) which was then methanolysed.[23] In marked contrast to 3-oxobutanoic acid (**1**), the acid (**6**) was not hygroscopic and was sufficiently stable to be recrystallised. Like the other β-oxo

Table 1. Reactions of aliphatic aldehydes with β-oxo acids

Aldehyde	β-Oxo acid	α,β-Unsaturated ketone	% Yield
EtCHO	(1)	(3)	70
Pr^{i}CHO	(1)	(4)	70
BuCHO	(1)	(5)	80
EtCHO	(6)	(9)	52
Bu^{i}CHO	(6)	(10)	57
Pr^{i}CHO	(12)	(13)	76
EtCHO	(15)	(16)	45
EtCHO	(17)	(18)	<5

Table 2. Percentage enol content for solutions of some β-oxo acids

Acid	% Enol in $CDCl_3$[a]	% Enol in CCl_4[a]
(1)	14[b]	46[c]
(6)	8	46
(12)	19	47
(15)	26	65
(17)	—	—

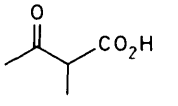
[a] Values were obtained by n.m.r. integration for dilute solutions at 37 °C. [b] Lit.,[17] 23.5% at 35 °C. [c] Lit.,[17] 49% at 35 °C.

acids prepared during the course of this work, compound (6) is in equilibrium with its enol tautomer when in solution. Table 2 shows the percentage enolisation for these compounds as estimated by n.m.r. for solutions in chloroform and in carbon tetrachloride. Condensation of the β-oxo acid (6) with propanal in pyridine yielded the expected (*E*)-hept-4-en-3-one (9).

In a similar way, condensation of 3-oxopentanoic acid (6) with 3-methylbutanal gave (*E*)-7-methyloct-4-en-3-one (10), a major constituent of the marine sponge *Plakortis zygompha*.[24] This perfume has been synthesized several times in the recent past.[25]

Acylation of (7) with isobutyryl chloride gave (11) which was methanolysed to 4-methyl-3-oxopentanoate. On hydrolysis this yielded 4-methyl-3-oxopentanoic acid (12). Compound (12) was alternatively synthesized from 3-methylbutan-2-one by ethoxycarbonylation of its sodium enolate followed by hydrolysis of the product ethyl 4-methyl-3-oxopentanoate. The acid (12) was obtained as an extremely hygroscopic solid. Condensation with 2-methylpropanal under the usual conditions gave (*E*)-2,6-dimethylhept-4-en-3-one (13) in good yield.

Acylation of Meldrum's acid (7) with 2-phenylacetyl chloride afforded (14) which was quantitatively methanolysed to methyl 3-oxo-4-phenylbutanoate. The usual hydrolysis gave the previously described[26] 3-oxo-4-phenylbutanoic acid (15) as a non-hygroscopic solid. Condensation of the β-oxo acid (15) with propanal yielded (*E*)-1-phenylhex-3-en-2-one (16).



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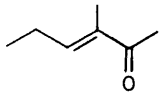

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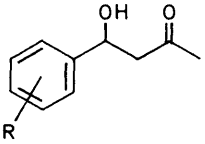
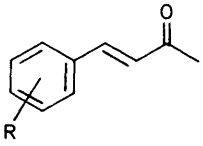


(19) R = 2-NO_2
(20) R = 4-NO_2
(21) R = 3-NO_2
(23) R = 4-Cl
(25) R = H

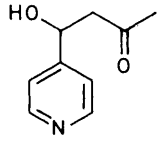


(22) R = 3-NO_2
(24) R = 4-Cl
(26) R = H
(27) R = 4-MeO

The reactions described above outline the use of β-oxo acids as regiospecific enol equivalents of methyl alkyl ketones. In an attempt to extend this synthesis of α,β-unsaturated ketones to α-branched systems, ethyl 2-methyl-3-oxobutanoate was hydrolysed to the liquid 2-methyl-3-oxobutanoic acid (17). This compound did not exhibit detectable enolisation in solution. Reaction of the β-oxo acid with propanal in pyridine, gave only very minor amounts of the expected 3-methylhex-3-en-2-one (18). We, thus, conclude that 2-alkyl-3-oxoalkanoic acids undergo decarboxylation faster than they can react with aldehydes under these conditions.

Attention then turned to the reaction of β-oxo acids with aromatic aldehydes. Treatment of 2-nitrobenzaldehyde with 3-oxobutanoic acid (1) gave exclusively the known[27] 4-hydroxy-4-(2′-nitrophenyl)butan-2-one (19) (Table 3). Similarly, 4-nitrobenzaldehyde yielded only the ketol (20).[28] Reaction of the β-oxo acid (1) with 3-nitrobenzaldehyde gave the corresponding β-ketol (21),[29] together with a minor amount of the enone (22). When compound (1) was treated with 4-chlorobenzaldehyde, both the ketol (23) and the enone (24) were formed. The β-ketol (23) was readily dehydrated to give the enone (24) and could not be recrystallised for analysis. Chromatography of the ketol (23) on silica gel led to its partial retro-aldolisation. The n.m.r. spectrum of compound (23), obtained for a dilute solution in carbon tetrachloride, exhibited the expected doublet and triplet absorptions for the methylene and methine protons of the side-chain. By contrast, a concentrated solution displayed an apparent triplet and a double doublet for these protons, suggesting the existence of some intermolecular association which restricts the rotational freedom of the alkyl chain.

Benzaldehyde reacted rather inefficiently with 3-oxobutanoic acid (1) to give 4-hydroxy-4-phenylbutan-2-one (25)[6] and the enone (26) in equal quantities. With 4-methoxybenzaldehyde, the only product, formed in poor yield, was the enone (27). This result is in agreement with that of Schöpf[6] who obtained the enone (27) from the reaction between sodium 3-oxobutanoate and 4-methoxybenzaldehyde under his experimental conditions. Reaction of compound (1) with pyridine 4-carbaldehyde gave exclusively the ketol (28). Like the chloro compound (23), the ketol (28) was readily dehydrated on handling. Finally, when 3-oxopentanoic acid (6) was treated with 4-nitrobenzaldehyde, the expected β-ketol (29)[30] was the sole product.



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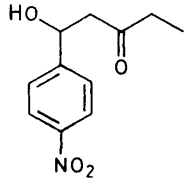


(29)

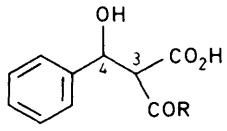
Table 3 shows clearly that there is a relationship between the degree of electron withdrawal from the aryl group, the product yield, and the ketol:enone ratios observed. The aldehydes which bear electronegative substituents give high yields of, predominantly, β-hydroxy ketones. The particular stability of such compounds where the aryl ring is nitro substituted has been previously discussed.[31–33] 4-Methoxybenzaldehyde reacts sluggishly with 3-oxobutanoic acid (1), affording only the α,β-unsaturated ketone. Benzaldehyde fits neatly between these two extremes, giving equal proportions of ketol and enone.

The classical Knoevenagel reaction of malonic acid with benzaldehyde in pyridine has been shown[34] to take place *via* formation of the intermediate (30) and then, predominantly, elimination of water to give benzylidenemalonic acid (31) which finally undergoes decarboxylation to yield compound (32). This decarboxylation is first-order, and its rate is identical with that

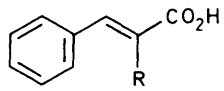
Table 3. Reactions of aromatic aldehydes with β-oxo acids

Aldehyde	β-Oxo acid	β-Ketol	Enone	Ratio[a]	% Yield[b]
2-Nitrobenzaldehyde	(1)	(19)	—	100:0	74
4-Nitrobenzaldehyde	(1)	(20)	—	100:0	53
3-Nitrobenzaldehyde	(1)	(21)	(22)	90:10	78
4-Chlorobenzaldehyde	(1)	(23)	(24)	80:20	72
Benzaldehyde	(1)	(25)	(26)	50:50	30
4-Methoxybenzaldehyde	(1)	—	(27)	0:100	10
Pyridine-4-carbaldehyde	(1)	(28)	—	100:0	83
4-Nitrobenzaldehyde	(6)	(29)	—	100:0	80

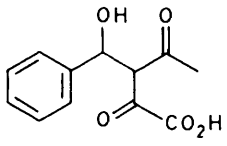
[a] Ratio of β-ketol to enone. [b] Yield of both products based on aldehyde; reaction mixtures were equimolar in β-oxo acid and aldehyde.



(30) R = OH
(33) R = Me



(31) R = CO_2H
(32) R = H



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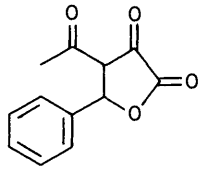

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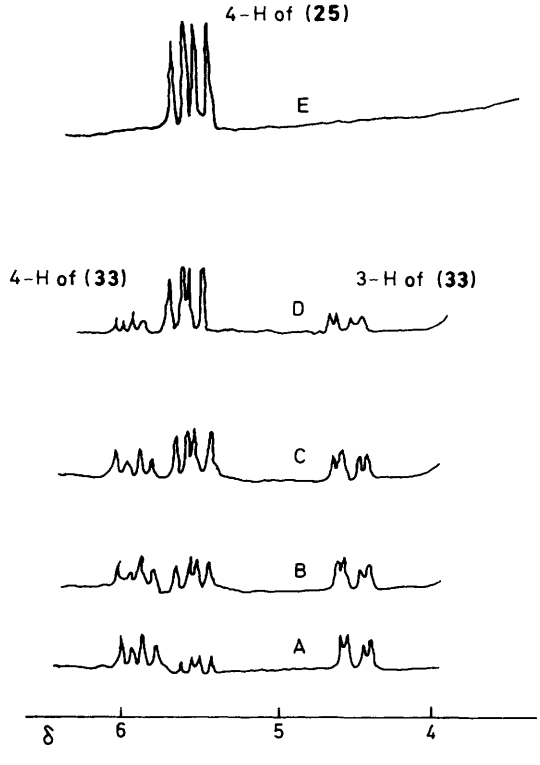

(1)

Figure. Reaction of 3-oxobutanoic acid (1) with benzaldehyde in pyridine after: A, 5 min; B, 11 min; C, 17 min; D, 26 min; E, 60 min (after heating to 80°C).

measured independently for compound (**31**) under the same conditions. We have now obtained evidence that the reaction of 3-oxobutanoic acid (**1**) with benzaldehyde in pyridine leads to the observed mixture of the β-hydroxy ketone (**25**) and the α,β-unsaturated ketone (**26**) by the sequence (**33**) ⟶ (**25**) ⟶ (**26**), *i.e.*, that dehydration is *subsequent* to decarboxylation.

3-Oxobutanoic acid (**1**) and benzaldehyde were dissolved in pyridine at 37 °C and the reaction was continuously monitored by n.m.r. spectroscopy. After a few minutes, signals not related to the reactants or to the final product appeared (Figure). At the outset, the integrated intensity of these peaks exceeded that of those assignable to 4-H of the β-ketol (**25**), and it remained constant as the reaction proceeded, finally declining as the concentration of β-oxo acid (**1**) reached low levels. These resonances were completely absent after the reaction mixture has been heated to 80 °C. We attribute the sets of signals centred near δ 5.8 and 4.3 to 3-H and 4-H, respectively, of the intermediate compound (**33**). A pair of doublets are seen for each of these protons owing to the relatively non-selective formation of *erythro* and *threo* isomers. A double resonance experiment confirmed that these multiplets are spin-coupled. An n.m.r. spectrum of authentic material confirmed that 4-H of the ketol (**25**) appears as a double doublet in pyridine solution.

An attempt was made to trap the intermediate compound (**33**) as its methyl ester, by quenching the reaction mixture with diazomethane, but this was unsuccessful. In an effort to obtain structure (**34**), which should be a more stable analogue of compound (**33**), 2,4-dioxopentanoic acid was exposed to benzaldehyde in pyridine but no observable reaction occurred. However, it is known[35] that ethyl 2,4-dioxopentanoate undergoes piperidine-catalysed condensation with benzaldehyde to yield the butanolide (**35**).

As might have been anticipated, 3-oxobutanoic acid (**1**) failed to condense with saturated ketones. The possibility of achieving conjugate addition to α,β-unsaturated systems was briefly examined. Although there are some literature precedents for this reaction,[36,37] 3-oxobutanoic acid (**1**) failed to add to but-3-en-2-one, ethyl prop-2-enoate, or 2-methyl-1,4-naphthoquinone under our conditions.

Experimental

I.r. spectra were measured for liquid films (L) or Nujol mulls (N) on a Perkin Elmer 298 instrument. N.m.r. spectra were recorded at 60 MHz using a JEOL PMX–60 spectrometer in the solvents indicated. Mass spectra were generally recorded using an AEI MS–30 instrument operating at 70 eV. Thin layer chromatography was carried out on Merck silica gel $60F_{254}$, while Merck silica gel 60PF was used for column chromatography. All m.p.s are uncorrected. Anhydrous magnesium sulphate was used for drying all organic solutions. 'The usual work-up' means extraction of organic products into diethyl ether or another specified solvent, washing, drying, and evapor-

ating. Elemental analyses were obtained from the Microanalytical Laboratory, University College, Dublin.

3-Oxobutanoic Acid (**1**).—Ethyl 3-oxobutanoate (19.5 g) was stirred overnight with water (150 ml) and sodium hydroxide (6.3 g). The reaction mixture was then placed in a separating funnel with an equal volume of ether and the aqueous layer saturated with ammonium sulphate. Sulphuric acid (4.2 ml), diluted with water (50 ml), was added and the funnel shaken. The ethereal layer was dried and then evaporated under reduced pressure, the temperature being kept below 30 °C. The liquid residue was then pumped at 0.5 mmHg to remove extraneous water. The crystalline product (9.5 g) was stored at −20 °C.

Hex-3-en-2-one (**3**).—3-Oxobutanoic acid (**1**) (1.0 g) was added to freshly distilled propanal (0.59 g) in pyridine (2 ml), and the mixture was left at 20 °C for 15 h. After being heated to 90 °C for 15 min, the mixture was added to an excess of dilute hydrochloric acid to remove pyridine and was then extracted with ether. The ethereal extract was washed with water and then with aqueous sodium hydrogen carbonate, dried, and distilled through a short fractionating column to give hex-3-en-2-one (**3**) (0.7 g), $\nu_{max.}$(L) 1 680, 1 634, 1 182, and 978 cm^{-1}; $\delta_H(CCl_4)$ 2.15 (3 H, s, CH_3CO), 5.95 (1 H, d, *J* 15.5 Hz, $COCH{=}CH$), 6.74 (1 H, t, *J* 15.5 and 5.5 Hz, $CH{=}CHCH_2$), 2.0 (2 H, m, CH_2CH_3), and 1.08 (3 H, t, *J* 7.5 Hz, CH_2CH_3).

5-Methylhex-3-en-2-one (**4**).—3-Oxobutanoic acid (**1**) (3.4 g) and 2-methylpropanal (2 g) in pyridine (5 ml) yielded 5-methylhex-3-en-2-one (**4**) (2.6 g),[38] $\nu_{max.}$(L) 1 672, 1 637, 1 460, 1 260, and 980 cm^{-1}, $\delta_H(CCl_4)$ 2.17 (3 H, s, CH_3CO), 5.94 (1 H, d, *J* 16.0 Hz, $COCH{=}CH$), 6.64 (1 H, dd, *J* 16.0 and 6.0 Hz, $COCH{=}CH$), 2.37 [1 H, m, $CH(CH_3)_2$], and 1.08 [6 H, d, *J* 6.0 Hz, $CH(CH_3)_2$].

Oct-3-en-2-one (**5**).—3-Oxobutanoic acid (**1**) (3.5 g), pentanal (2.95 g), and pyridine (3 ml) yielded oct-3-en-2-one (**5**)[39] (3.44 g); $\nu_{max.}$(L) 1 672, 1 620, 1 360, 1 252, 1 170, and 980 cm^{-1}, $\delta_H(CCl_4)$ 2.29 (3 H, s, CH_3CO), 5.99 (1 H, d, *J* 16.0 Hz, $COCH{=}CH$), 6.69 (1 H, dt, *J* 16.0 and 7.0 Hz, $COCH{=}CH$), 2.2 (2 H, m, $CH{=}CHCH_2$), 1.4 (4 H, m, $CH_2CH_2CH_3$), and 0.9 (3 H, m, virtual coupling, CH_2CH_3).

3-Oxopentanoic Acid (**6**).—2,2-Dimethyl-5-propionyl-1,3-dioxane-4,6-dione (**8**) was prepared according to the method of Oikawa *et al.*,[23] and methanolysed in refluxing methanol to give methyl 3-oxopentanoate (87% overall yield). The ester (7.8 g) was stirred overnight with water (60 ml) and sodium hydroxide (2.52 g). Work-up as described above for the case of 3-oxobutanoic acid (**1**) gave the *acid* (**6**) as a solid (4.66 g, 67%) which could be recrystallised from ether–hexane to give *needles*, m.p. 65—66 °C (decomp.) $\delta_H(CCl_4)$ keto tautomer 1.08 (3 H, t, *J* 7.8 Hz, CH_2CH_3), 2.55 (2 H, q, *J* 7.8 Hz, CH_2CH_3), 3.37 (2 H, s, $COCH_2CO_2H$), 10.9 (1 H, br, s, exch. D_2O, CO_2H), enol tautomer 1.15 (3 H, t, *J* 7.8 Hz, CH_2CH_3), 2.25 (2 H, q, *J* 7.8 Hz, CH_2CH_3), 4.95 [1 H, s, $C(OH){=}CHCO_2H$], and 11.8 [1 H, br, s, $C(OH){=}CH$]; $\delta_H(CDCl_3)$ keto tautomer 1.09 (3 H, t, *J* 7.1 Hz, CH_2CH_3), 2.59 (2 H, q, *J* 7.1 Hz, CH_2CH_3), 3.49 (2 H, s, $COCH_2CO_2H$), 7.89 (1 H, br, s, exch. D_2O, CO_2H), enol tautomer 5.00 [1 H, s, $C(OH){=}CHCO_2H$].

Hept-4-en-3-one (**9**).—3-Oxopentanoic acid (**6**) (2.8 g) was added to a solution of propanal (1.45 g) in pyridine (2 ml). After the usual reaction time and work-up, the product was obtained as an oil[40] (1.4 g), $\nu_{max.}$(L) 1 670, 1 620, 1 460, 1 195, 975, and 875 cm^{-1}; $\delta_H(CDCl_3)$ 1.06 (3 H, t, *J* 7.2 Hz, $COCH_2CH_3$), 2.52 (2 H, q, *J* 7.2 Hz, $COCH_2CH_3$), 5.99 (1 H, d, *J* 15.9 Hz, $COCH{=}CH$), 6.76 (1 H, dt, *J* 15.9 and 6.08 Hz, $COCH{=}CH$), and 1.00 (3 H, $CH{=}CHCH_2CH_3$).

7-Methyloct-4-en-3-one (**10**).—3-Oxopentanoic acid (**6**) (3.32 g) was added to 3-methylbutanal (1.72 g) in pyridine (3 ml). The usual work-up yielded the ketone (**10**)[24] (1.6 g) as an oil, $\nu_{max.}$(L) 1 668, 1 625, 1 192, and 978 cm^{-1}; $\delta_H(CDCl_3)$ 0.90 [6 H, d, *J* 6.5 Hz, $CH(CH_3)_2$], 0.98 (3 H, t, *J* 7.0 Hz, CH_2CH_3), 2.45 (2 H, q, *J* 7.0 Hz, CH_2CH_3), 5.95 (1 H, d, *J* 16.0 Hz, $COCH{=}CH$), and 6.72 (1 H, dt, *J* 16.0 and 7.0 Hz, $COCH{=}CHCH_2$).

4-Methyl-3-oxopentanoic Acid (**12**).—A solution of Meldrum's acid (10.0 g) in dichloromethane (50 ml) and pyridine (11 ml) was cooled to −5 °C, and 2-methylpropanoyl chloride (7.4 g) was added with stirring. After 1 h at 0 °C and a further 1 h at room temperature, work up[23] yielded 2,2-dimethyl-5-(2-methylpropionyl)-1,3-dioxane-4,6-dione (**11**) (10.6 g) (71%) as an oil which was not further purified, $\nu_{max.}$(L) 1 810, 1 725, 1 660, 1 575, 1 330, 1 202, 1 150, 1 020, 920, and 807 cm^{-1}; $\delta_H(CDCl_3)$ 1.21 [6 H, d, *J* 6.63 Hz, $CH(CH_3)_2$], 4.07 [1 H, septet, *J* 6.63 Hz, $CH(CH_3)_2$], and 1.70 (6 H, s, *gem*-dimethyl). The crude acyl derivative (**11**) (10.5 g) was refluxed during 4 h with methanol (100 ml). The product, methyl 4-methyl-3-oxopentanoate was obtained as an oil (4.9 g), $\nu_{max.}$(L) 1 750, 1 715, 1 315, 1 160, and 1 005 cm^{-1}; $\delta_H(CCl_4)$ 1.13 [6 H, d, *J* 6.95 Hz, $CH(CH_3)_2$], 2.74 [1 H, septet, *J* 6.95 Hz, $CH(CH_3)_2$], 3.51 (2 H, s, $COCH_2CO_2$), and 3.70 (3 H, s, CO_2CH_3). The ester (4.4 g) was then dissolved in water (50 ml) containing sodium hydroxide (3.66 g). After 12 h, the usual work-up afforded the desired 4-methyl-3-oxopentanoic acid (**12**) (2.5 g) as a *hygroscopic solid*: $\delta_H(CCl_4)$ keto tautomer 1.09 [6 H, d, *J* 7.3 Hz, $CH(CH_3)_2$], 2.55 [1 H, septet, *J* 7.3 Hz, $CH(CH_3)_2$], 3.45 (2 H, s, $COCH_2CO_2H$), 11.75 (1 H, br, s, exch. D_2O, CO_2H), enol tautomer 1.12 [6 H, d, *J* 7.3 Hz, $CH(CH_3)_2$], 2.4 [1 H, septet, *J* 7.3 Hz, $CH(CH_3)_2$], and 4.93 (1 H, s, $C(OH){=}CHCO_2$); $\delta_H(CDCl_3)$ keto tautomer 1.14 [6 H, d, *J* 7.0 Hz, $CH(CH_3)_2$], 2.72 [1 H, septet, *J* 7.0 Hz, $CH(CH_3)_2$], 3.52 (2 H, s, $COCH_2CO_2$), 10.75 (1 H, br, s, exch. D_2O, CO_2H), enol tautomer 1.14 ([6 H, d, *J* 7.0 Hz, $CH(CH_3)_2$], *ca.* 2.5 [1 H, septet, *J* 7.0 Hz, $CH(CH_3)_2$], and 4.95 [1 H, s, $C(OH){=}CHCO_2$].

2,6-Dimethylhept-4-en-3-one (**13**).—4-Methyl-3-oxopentanoic acid (**12**) (10.5 g) was treated with 2-methylpropanal (5.8 g) in pyridine (16 ml). The usual treatment then afforded 2,6-dimethylhept-4-en-3-one (**13**)[41] (8.6 g), $\nu_{max.}$(L) 1 675, 1 632, 1 212, 1 063, and 980 cm^{-1}; $\delta_H(CCl_4)$ 1.10 [6 H, d, *J* 6.8 Hz, $COCH(CH_3)_2$], 2.80 [1 H, septet, *J* 6.8 Hz, $CH(CH_3)_2$], 5.98 (1 H, d, *J* 16.0 Hz, $COCH{=}CH$), 6.67 (1 H, dd, *J* 16.0 and 6.75 Hz, $COCH{=}CH$), 2.63 [1 H, m, *J* 6.75 and 6.9 Hz, $CH{=}CHCH(CH_3)_2$], and 1.08 [6 H, d, *J* 6.9 Hz, $CH{=}CHCH(CH_3)_2$].

3-Oxo-4-phenylbutanoic Acid (**15**).—2,2-Dimethyl-5-phenylacetyl-1,3-dioxane-4,6-dione (**14**)[23] was methanolysed to give methyl 3-oxo-4-phenylbutanoate. This ester (7.6 g) was hydrolysed in water (30 ml) with sodium hydroxide (2.5 g) and sufficient ethanol to give a homogeneous solution. The usual work-up led to the solid 3-oxo-4-phenylbutanoic acid (**15**) (6.7 g),[26] $\delta_H(CCl_4)$ keto tautomer 7.17 (5 H, s, C_6H_5), 3.32 (2 H, s, $CH_2C_6H_5$), 3.72 (2 H, s, $COCH_2CO_2$), 10.9 (1 H, br, s, exch. D_2O, CO_2H), enol tautomer 7.17 (5 H, s, C_6H_5), *ca.* 3.5 (2 H, app. q, $CH_2C_6H_5$), 4.87 (1 H, s, $C(OH){=}CHCO_2H$); $\delta_H(CDCl_3)$ keto tautomer 7.26 (5 H, br, s, C_6H_5), 3.49 (2 H, s, $CH_2C_6H_5$), 3.81 (2 H, s, $COCH_2CO_2$), enol tautomer 7.26 (5 H, br, s, C_6H_5), 3.61 and 3.55 (2 H, AB q, J_{gem} 13.43 Hz, $CH_2C_6H_5$), and 4.94 (1 H, s, $C(OH){=}CH$).

1-*Phenylhex*-3-*en*-2-*one* (**16**).—Addition of 3-oxo-4-phenylbutanoic acid (**15**) (2.0 g) to a solution of propanal (1 g) in pyridine (2 ml) yielded an oily product (0.9 g) which (n.m.r.) was 1-phenylhex-3-en-2-one (**16**) contaminated with a small amount of 1-phenylbutan-2-one, the product of the keto acid decarboxylation. The enone had $\nu_{max.}$(L) 1 710, 1 620, 975, 735, and 700 cm^{-1}; $\delta_H(CDCl_3)$ 7.25 (5 H, br, s, C_6H_5), 3.81 (2 H, s, $CH_2C_6H_5$), 6.14 (1 H, d, *J* 16.35 Hz, COC*H*=CH), 6.97 (1 H, m, *J* 16.35 and 6.5 Hz, COCH=*CH*), 2.21 (2 H, m, *J* 6.5 and 7.3 Hz, CH=CHCH_2), and 1.04 (3 H, t, *J* 7.3 Hz, CH_2CH_3).

2-*Methyl*-3-*oxobutanoic Acid* (**17**).—Ethyl 3-oxobutanoate (50 g) was alkylated with methyl iodide in the presence of sodium ethoxide to give ethyl 2-methyl-3-oxobutanoate (39.9 g) as an oil,[42] b.p. 45—48 °C/0.2 mmHg. This ester (9.7 g) was hydrolysed with sodium hydroxide (3.15 g) in water (70 ml) to give 2-methyl-3-oxobutanoic acid (**17**) (5.0 g) as an oil which failed to solidify, $\delta_H(CDCl_3)$ 2.28 (3 H, s, COCH_3), 3.59 [1 H, q, *J* 7.0 Hz, C*H*(CH_3)], 1.36 [3 H, d, *J* 7.0 Hz, CH(CH_3)], and 11.22 (1 H, br, s, exch. D_2O, CO_2H).

4-*Hydroxy*-4-(2-*nitrophenyl*)*butan*-2-*one* (**19**).—3-Oxobutanoic acid (**1**) (1.0 g) was added to a solution of 2-nitrobenzaldehyde (1.48 g) in pyridine (4 ml). After the usual reaction time and work-up, the crude product was obtained as an oil (1.91 g) which (n.m.r.) contained the ketol (**19**) (80%) together with some unchanged aldehyde. Column chromatography on silica gel using dichloromethane–hexane as eluant gave pure ketol, m.p. 65—68 °C (CH_2Cl_2–hexane), lit.,[27] m.p. 68—69 °C, $\nu_{max.}$(N) 3 150, 1 710, 1 520, 1 332, and 740 cm^{-1}; $\delta_H(CCl_4)$ 7.2—8.0 (4 H, m, aryl), 5.76 (1 H, dd, *J* 8.0 and 3.0 Hz, C*H*(OH)CH_2), 3.40 (1 H, br, s, exch. D_2O, OH), 2.50 (1 H, m, *J* 8.0 and 17.5 Hz, CH_2CO), 3.29 (1 H, m, *J* 3.0 and 17.5 Hz, CH_2CO), and 2.20 (3 H, s, COCH_3).

4-*Hydroxy*-4-(4-*nitrophenyl*)*butan*-2-*one* (**20**).—A mixture of 3-oxobutanoic acid (**1**) (1.63 g), pyridine (10 ml), and 4-nitrobenzaldehyde (2.41 g) yielded, after the usual treatment, a solid product (1.85 g) which was recrystallised from benzene–hexane to give 4-hydroxy-4-(4-nitrophenyl)butan-2-one (**20**) (1.75 g) as colourless needles which had m.p. 60—62 °C, (lit.,[28] m.p. 58 °C), and $\nu_{max.}$(N) 3 415, 1 705, 1 510, 1 340, and 860 cm^{-1}; $\delta_H(CDCl_3)$ 8.12 (2 H, d, *J* 9.0 Hz, 3- and 5-ArH), 7.47 (2 H, d, *J* 9.0 Hz, 2- and 6-ArH), 5.16 [1 H, t after D_2O exch., *J* 6.0 Hz, C*H*(OH)], 2.84 [2 H, d, *J* 6.0 Hz, CH(OH)CH_2], and 2.22 (3 H, s, $COCH_3$); *m*/*z* 209 (M^+), 191, 176, 150, 134, 105, 77, 58, and 43.

4-*Hydroxy*-4-(3-*nitrophenyl*)*butan*-2-*one* (**21**) *and* 4-(3-*Nitrophenyl*)*but*-3-*en*-2-*one* (**22**).—A mixture of 3-oxobutanoic acid (**1**) (1.04 g), pyridine (4 ml), and 3-nitrobenzaldehyde (1.48 g) yielded, after work-up, a pale yellow oil (1.62 g) which (n.m.r.) contained a 90:10 mixture of the ketol (**21**) and the enone (**22**). These products were separated by column chromatography on silica gel using CH_2Cl_2–hexane as eluant when 4-hydroxy-4-(3-nitrophenyl)butan-2-one (**21**) was obtained as an oil,[28] $\nu_{max.}$(L) 3 430, 1 705, 1 525, 1 350, 810, and 730 cm^{-1}; $\delta_H(CCl_4)$ 7.3—8.3 (4 H, m, aryl), 5.25 [1 H, t, *J* 6.0 Hz, C*H*(OH)], 3.83 (1 H, br, s, exch. D_2O, OH), 2.90 [2 H, d, *J* 6.0 Hz, CH(OH)CH_2], and 2.18 (3 H, s, $COCH_3$); *m*/*z* 209 (M^+), 191, 176, 151, 150, 105, 77, 58, 51, and 43. The 4-(3-nitrophenyl)but-3-en-2-one (**22**) was eluted from the column prior to the ketol (**21**), and was a low-melting solid which had $\delta_H(CCl_4)$ 7.5—8.5 (4 H, m, ArH), 7.47 (1 H, d, *J* 16.0 Hz, C*H*=CHCO), 6.77 (1 H, d, *J* 16.0 Hz, CH=C*H*CO), and 2.37 (3 H, s, $COCH_3$).

4-(4-*Chlorophenyl*)-4-*hydroxybutan*-2-*one* (**23**) *and* 4-(4-*Chlorophenyl*)*but*-3-*en*-2-*one* (**24**).—The reaction of 3-oxobutanoic acid (**1**) (6.1 g) with 4-chlorobenzaldehyde (8.4 g) in pyridine (10 ml) yielded an oil (10.85 g), which contained (n.m.r.) ketol (60%), enone (20%), and unchanged aldehyde (20%). These components were separated by column chromatography on silica gel using CH_2Cl_2–hexane as eluant. 4-(4-*Chlorophenylbut*-3-*en*-2-*one* (**24**) was obtained as *needles* from CH_2Cl_2–hexane, m.p. 57.5—58 °C, $\nu_{max.}$(N) 1 655, 1 590, 1 090, and 980 cm^{-1}; $\delta_H(CCl_4)$ 7.39 (4 H, s, ArH), 7.34 (1 H, d, *J* 16.0 Hz, C*H*=CHCO), 6.59 (1 H, d, *J* 16.0 Hz, CH=C*H*CO), and 2.28 (3 H, s, COCH_3); *m*/*z* 182/180, 167/165, 145, 139/137, 102, 101, 75, 51, and 43 (Found C, 66.2, H, 4.75%. Calc. for: C, 66.48; H, 4.98%.)

4-(4-*Chlorophenyl*)-4-*hydroxybutan*-2-*one* (**23**) was obtained as a *solid*, m.p. 36—37.5 °C, which underwent dehydration to the enone (**24**) on attempted crystallisation; $\nu_{max.}$(N) 3 340, 1 700, 1 072, and 820 cm^{-1}; $\delta_H(CCl_4)$ 7.20 (4 H, br, s, ArH), 5.00 [1 H, dd, *J* 7.0 and 5.0 Hz, C*H*(OH)], 3.55 (1 H, br, s, exch. D_2O, OH), 2.67 [2 H, app. t, *J* 5.0 and 7.0 Hz, CH(OH)CH_2], and 2.10 (3 H, s, $COCH_3$). Attempts to obtain an exact molecular ion by high-resolution mass spectrometry failed; dehydration took place to give the enone [Found: 180.0336. Calc. for: $C_{10}H_9ClO$($C_{10}H_{11}ClO_2 - H_2O$), 180.0339].

Reaction of 3-*Oxobutanoic Acid* (**1**) *with Benzaldehyde*.—A mixture of 3-oxobutanoic acid (**1**) (3.5 g), benzaldehyde (3.63 g), and pyridine (4 ml) yielded an oil (4.2 g) which (n.m.r.) contained unchanged aldehyde (70%), ketol (15%), and enone (15%). These compounds were separated by column chromatography in the usual way. 4-Phenylbut-3-en-2-one (**26**) was identical with an authentic specimen. 4-Hydroxy-4-phenylbutan-2-one (**25**):[6] $\delta_H(CCl_4)$ 7.17 (5 H, br, s, ArH), 3.78 (1 H, br, s, exch. D_2O, OH), 4.95 [1 H, dd, *J* 7.0 and 5.5 Hz, C*H*(OH)], 2.63 [2 H, dd, *J* 7.0 and 5.5 Hz, CH(OH)CH_2], and 2.00 (3 H, s, $COCH_3$).

Reaction of 3-*Oxobutanoic Acid* (**1**) *with* 4-*Methoxybenzaldehyde*.—The acid (**1**) (4.4 g) was allowed to react under the usual conditions with 4-methoxybenzaldehyde (5.69 g) in pyridine (6 ml). Work-up gave an oil (5.7 g) which (n.m.r.) consisted of unchanged aldehyde (90%) and 4-(4-methoxyphenyl)but-3-en-2-one (**27**) (10%). This material was not isolated. No signals attributable to the corresponding ketol were seen.

4-*Hydroxy*-4-(4-*pyridyl*)*butan*-2-*one* (**28**).—3-Oxobutanoic acid (**1**) (5.0 g) was allowed to react directly with pyridine-4-carbaldehyde (5.24 g). After 12 h, the mixture was diluted with ether and the extract washed with water. After drying and evaporation, the product was obtained as an oil which failed to solidify (6.7 g, 83%). Attempted purification by distillation led to partial dehydration to the related enone. The ketol (**28**) had $\nu_{max.}$(L) 3 190, 1 605, 1 480, 1 170, 1 080, 1 013, and 760 cm^{-1}; $\delta_H(CDCl_3)$ 8.35 (2 H, d, *J* 6.0 Hz, 3- and 5-pyridyl H), 7.27 (2 H, d, *J* 6.0 Hz, 2- and 6-pyridyl H), 5.11 [1 H, dd, *J* 6.8 and 7.8 Hz, C*H*(OH)], 2.60 [2 H, dd, *J* 6.8 and 7.8 Hz, –CH(OH)CH_2], 4.83 (1 H, br, s, exch. D_2O, OH), and 2.17 (3 H, s, –$COCH_3$). (Found: 165.0785. Calc. for: $C_9H_{11}NO_2$ *m*/*z* 165.0787.)

1-*Hydroxy*-1-(4-*nitrophenyl*)*pentan*-3-*one*.—3-Oxopentanoic acid (**6**) (0.6 g), 4-nitrobenzaldehyde (0.78 g), and pyridine (6 ml) were allowed to react together to give 1-*hydroxy*-1-(4-*nitrophenyl*)*pentan*-3-*one* (**29**) (1.25 g) which formed needles from CH_2Cl_2–hexane, m.p. 91.5—92 °C, $\nu_{max.}$(N) 3 525, 1 705, 1 602, 1 510, 1 340, 1 202, 1 115, 1 085, 845, 790, 750, 740, and 700 cm^{-1}; $\delta_H(CDCl_3)$ 8.09 (2 H, d, *J* 8.5 Hz, 3- and 5-ArH), 7.47 (2 H, d, *J* 8.5 Hz, 2- and 6-ArH), 5.22 [1 H, t, *J* 6.2 Hz, C*H*(OH)], 3.70 (1 H, br s, exch. D_2O, OH), 2.81 [2 H, d, *J* 6.2 Hz, CH(OH)CH_2], 2.47 (2 H, q, *J* 7.06 Hz, CH_2CH_3), and 1.09 (3 H, t, *J* 7.06 Hz, CH_2CH_3) (Found: C, 59.15; H, 5.7. $C_{11}H_{13}NO_4$ requires C, 59.18; H, 5.87%.)

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References

1 E. Knoevenagel, *Chem. Ber.*, 1896, **29**, 172.
2 G. Jones, *Org. React.*, 1967, **15**, 249.
3 A. M. Verley, *Bull. Soc. Chim. Fr.*, 1899, **21**, 414.
4 R. Robinson, *J. Chem. Soc.*, 1917, 762.
5 C. Schöpf, G. Lehmann, and W. Arnold, *Angew. Chem.*, 1937, **50**, 783.
6 C. Schöpf and K. Thierfelder, *Justus Liebigs Ann. Chem.*, 1935, **518**, 127.
7 M. Henze, *Z. Physiol. Chem.*, 1930, **189**, 121.
8 M. Henze and R. Muller, *Z. Physiol. Chem.*, 1930, **193**, 88.
9 R. Stöhr and M. Henze, *Z. Physiol. Chem.*, 1935, **206**, 1.
10 R. Stöhr, *Z. Physiol. Chem.*, 1935, **235**, 265.
11 R. Stöhr, *Z. Physiol. Chem.*, 1936, **240**, 23.
12 C. Neuberg and J. Burkard, *Biochem. Z.*, 1932, **253**, 222.
13 T. E. Friedemann, *J. Biol. Chem.*, 1925, **63**, xxi.
14 M. C. Nath, *Proc. Soc. Biol. Chem. (India)*, 1956, **15**, 42.
15 F. J. L. Aparicio, M. G. Guillen, and I. I. Cubero, *An. Quim.*, 1976, **72**, 938.
16 R. C. Kreuger, *J. Am. Chem. Soc.*, 1952, **74**, 5536.
17 K. D. Grande and S. M. Rosenfeld, *J. Org. Chem.*, 1980, **45**, 1626.
18 D. H. Grayson and M. R. J. Tuite, to be published.
19 D. O. Cheng and E. LeGoff, *Tetrahedron Lett.*, 1977, 1469.
20 S. Tsuboi, T. Uno, and A. Takeda, *Chem. Lett.*, 1978, 1325.
21 K. Uehara, F. Kitimura, and M. Tanaka, *Chem. Lett.*, 1973, 279.
22 J. E. Dubois, *Ann. Chim. (Paris)*, 1951, **6**, 406.
23 Y. Oikawa, K. Sugaro, and O. Yonemitsu, *J. Org. Chem.*, 1978, **43**, 2087.
24 D. J. Faulkner and B. N. Ravi, *Tetrahedron Lett.*, 1980, **21**, 23.
25 C. L. Bumgardner, J. R. Lever, and S. T. Purrington, *Tetrahedron Lett.*, 1982, **23**, 2379; J. Duran, J. Elliott, A. B. McElroy, and S. G. Warren, *ibid.*, 1983, **24**, 3927; I. Matsuda, H. Okada, S. Sato, and U. Izumi, *ibid.*, 1984, **25**, 3879.
26 B. Angelo, *C.R. Acad. Sci., Ser. C*, 1973, **276**, 293.
27 A. Baeyer and V. Drewson, *Chem. Ber.*, 1882, **15**, 2856.
28 A. Baeyer and P. Becker, *Chem. Ber.*, 1883, **16**, 1968.
29 W. Kraszewski and B. Weicowna, *Rocz. Chem.*, 1935, 15, 506.
30 M. Stiles, D. Wolf, and G. V. Hudson, *J. Am. Chem. Soc.*, 1959, **81**, 629.
31 J. Thiele, *Chem. Ber.*, 1899, **32**, 1293.
32 L. Bouveault and A. Wahl, *C.R. Acad. Sci.*, 1902, **135**, 41.
33 L. F. Fieser and W. H. Daubt, *J. Am. Chem. Soc.*, 1946, **68**, 2248.
34 S. Patai, J. Edlitz-Pfeffermann, and Z. Rozner, *J. Am. Chem. Soc.*, 1954, **76**, 3446.
35 O. Mumm, *Chem. Ber.*, 1912, **45**, 3236.
36 M. Yasuda, *Chem. Lett.*, 1975, 89.
37 M. Fuju, Y. Teroo, and M. Sekiya, *Chem. Pharm. Bull.*, 1974, **22**, 2675.
38 R. Bartlet, M. Montagne, and P. Arnaud, *Spectrochim. Acta, Part A*, 1980, **25**, 1626.
39 R. Heilman, G. de Gaudemaris, and P. Arnaud, *Bull. Soc. Chim. Fr.*, 1957, 119.
40 M. Andrac, *Ann. Chim.*, 1964, **9**, 287.
41 H. Thoms and H. Kahre, *Arch. Pharm. (Weinheim, Ger.)*, 1925, **263**, 241.
42 A. G. Gonzalez, J. M. Aguiar, J. D. Martin, and M. L. Rodriguez, *Tetrahedron Lett.*, 1976, 205.

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