The Acylation of β-Keto Ester Dianions

STUART NICHOLAS HUCKIN AND LARRY WEILER[1]

Department of Chemistry, University of British Columbia, Vancouver 8, British Columbia

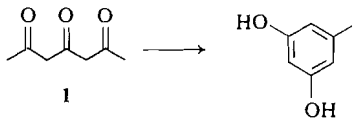
Received October 31, 1973

A method for the successful acylation of the dianion of simple β-keto esters to yield β,δ-diketo esters has been developed. The dianion of methyl acetoacetate also reacts with the monoanion of methyl acetoacetate to give a triketo ester which cyclizes to methyl orsellinate. These dianions also add to nitriles to give 5-amino-3-keto-4-pentenoates which may in some cases cyclize to 4-hydroxypyridones.

On a mis au point une méthode qui permet l'acylation des dianions de β-céto esters simples afin d'obtenir des β,δ-dicéto esters. Le dianion de l'acétoacétate de méthyle réagit aussi avec le monoanion de l'acétoacétate de méthyle pour donner un ester tricétonique qui se cyclise pour fournir l'orsellinate de méthyle. Ces dianions s'additionne aussi aux nitriles pour fournir les amino-5 céto-3 penténoates qui dans certains cas se cyclisent en hydroxy-4 pyridones. [Traduit par le journal]

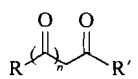
Can. J. Chem., **52**, 1343 (1974)

The acylation of the dianion of β-diketones has been the subject of several investigations in the past decade or so (1–9). This has been the most extensively investigated reaction of carbonyl multiple carbanions but it has also proved to be the most challenging and difficult to achieve in good yield. The interest in this reaction stems from the postulated intermediacy of β-polyketones in the biosynthesis of phenolic compounds (10, 11). The initial report which indicated the polycarbonyl origin of some phenolic compounds was the observation that heptane-2,4,6-trione (**1**) cyclizes to orcinol (**2**) (12), which was later confirmed by other workers (13, 14).



1 **2**

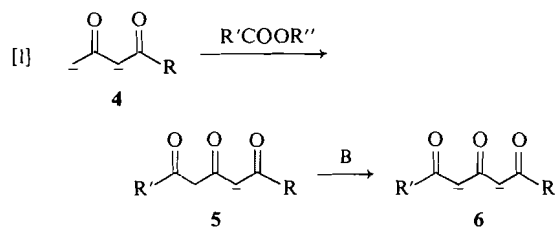
The laboratory synthesis of these postulated biosynthetic intermediates (**3**) has developed



3

along two separate lines. One approach has involved the synthesis of polycarbonyl compounds in which the reactivity of the ketone groups is protected as a pyrone (15–18). The second approach has involved the direct synthesis of polycarbonyl compounds involving acylation of the multiple carbanions of smaller polycarbonyl precursors (7, 9). The results of both routes indicate that the conversion of either protected analogs of **3** or the acyclic compounds (**3**) to phenolic compounds is possible.

The major difficulty in the acylation of the dianion from a β-diketone, for example **4**, arises from the fact that the intial condensation product **5** possesses a more acidic proton than the



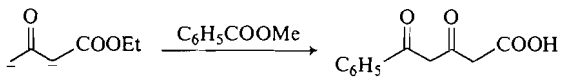
4 **5** **6**

monoanion of the starting material. Thus a proton will be transferred from the monoanion **5** to the dianion **4** to give the dianion **6**. Since the alkoxide that is formed during the condensation is not a sufficiently strong base to regenerate the dianion **4** from the corresponding monoanion, the maximum yield of product, based on the β-diketone, is 50%. In the initial acylations of β-keto dianions an excess of dianion was used (1); however, this approach would be unsatisfactory in a synthetic sequence in which the diketone is a valuable reagent. Addition of excess base, such as the metal amides, to these

[1]Author to whom correspondence should be addressed.

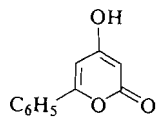
reactions often had deleterious effects (3) and occasionally improved the yield of triketone **6** (2). The yield of aroylation product (**6**, R″ = Aryl) can be very good using sodium hydride as the base in reaction 1 (5). However, this method is apparently limited to aroylations only. Similarly, acylation of the dianion of β-keto aldehydes is limited to aromatic esters (8).

Prior to our work (19) the only reported acylation of the dianion of a β-keto ester involved condensation of dianion **7** with methyl benzoate to give acid **8** or pyrone **9**, in 48 and 11% respectively, depending on the reaction conditions (20). Earlier we had developed a very



7 **8**

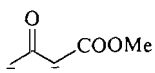
or



9

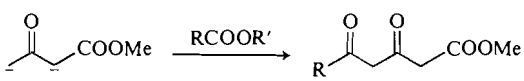
efficient method to generate the dianion of a range of β-keto esters (21). This involved treatment of the β-keto ester with 1 equiv. of sodium hydride followed by 1 equiv. of *n*-butyllithium or, alternately, with 2 equiv. of lithium diisopropylamide to produce the dianion of the β-keto ester. It was found that these intermediates undergo a variety of carbanion-type reactions to produce several novel and useful compounds (19, 21, 22).

In our initial studies it was found that the dianion **10** from methyl acetoacetate reacts violently with acyl halides even at −78 °C and



10

this reaction gave a complex mixture of products. Accordingly, less reactive acylating agents were investigated and it was found that dianion **10** reacts smoothly at 0 °C to give β,δ-diketo esters **11**. However, the yield in these condensations was not satisfactory (30–40%) in spite of their simplicity. No doubt one of the compli-



10 **11**

cations in this reaction was proton transfer from the monoanion of **11** to dianion **10** (*vide supra*).

Attempts to overcome this difficulty by employing an additional equivalent of base in the reaction were not successful, as any base strong enough to form the dianion was also sufficiently nucleophilic to attack the ester. For example lithium diisopropylamide and lithium *N*-isopropylcyclohexyl amide produced no reaction of dianion **10** with methyl acetate, whereas with methyl benzoate, good yields of the corresponding amides were obtained. The formation of these carboxamides was not unexpected (23). Hopefully the use of the recently reported H^+ arpoon bases would obviate this difficulty (24) but this has not been investigated to date.

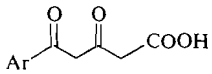
It was then envisaged that the degree of conversion of dianion **10** to diketo ester **11** could be raised, if, after the addition of ½ equiv. of the ester, the quenched dianion was regenerated by addition of more base before adding further ester. Three equivalents of base are required for complete conversion of dianion **10** to **11**. But, after addition of ½ equiv. of ester, only ½ equiv. of base is needed to fully regenerate the dianion **10**. Such an addition would raise the maximum theoretical yield to 75%, whereupon addition of ¼ equiv. of base would regenerate the dianion **10** completely. While it is possible that alternate additions of ester and base in ever decreasing amounts would eventually give complete conversion of dianion to diketo ester **11**, such a procedure would be very time consuming and tedious. It was found that reaction of dianion **10** with ½ equiv. of ester, followed by addition of ½ equiv. of *n*-butyllithium and finally by a further ½ equiv. of ester, did give yields of **11** in excess of 50%.

Then it was adventitiously discovered that addition of 1 equiv. of base, after the addition of the first portion of ester, gave even higher yields of **11**. Thus the most convenient procedure involved reaction of dianion **10** with ½ equiv. of ester, addition of 1 equiv. more of base, and finally the remaining ½ equiv. of ester. In this manner, reaction of **10** with methyl acetate gave methyl 3,5-dioxohexanoate (**11**, R = Me) in 71% yield and with methyl butanoate gave methyl 3,5-dioxooctanoate (**11**, R = *n*-Pr) in 67% yield.

The product **11** (R = H), arising from the condensation of dianion **10** and methyl formate,

decomposed on all attempts to purify it and was consequently characterized by spectral data only. When the dianion **10** was reacted with ethyl butanoate a mixture of methyl and ethyl 3,5-dioxooctanoate was isolated, the latter product arising from transesterification during the reaction. To avoid this complication all subsequent reactions were performed with methyl esters.

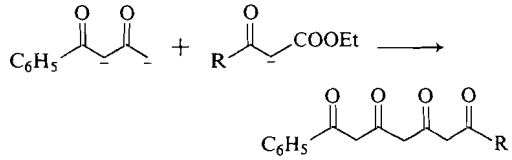
It was also found that the yields of the diketo esters from the condensation of aromatic esters with dianion **10** were low. Reinvestigation of the crude product from these reactions revealed that the corresponding carboxylic acid **12** was formed



12

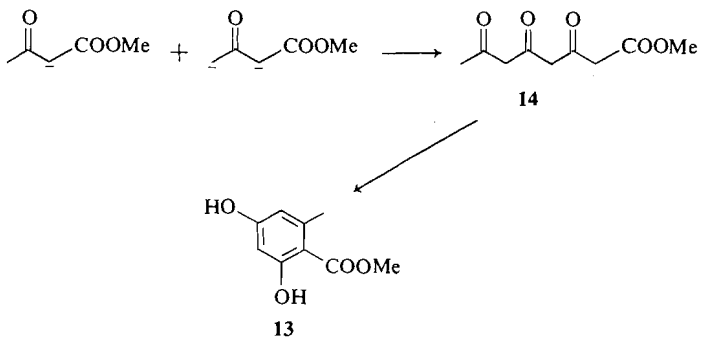
in significant amounts. We could only detect carboxylic acid products in the condensations with aromatic esters. Wolfe *et al.* were able to isolate only the carboxylic acid **12** (Ar = C_6H_5) from the aroylation of ethyl acetoacetate with methyl benzoate using sodium hydride in 1,2-dimethoxyethane (20). The mechanism of this hydrolysis, in both cases, remains obscure.

Recently it has been reported that very powerful nucleophiles, such as di- and trianions, react with the monoanions of β-keto esters to yield the acylated product (25). For example, it was possible to condense the dianion of 1-phenylbutane-1,3-dione with the monoanion of ethyl benzoylacetate and ethyl acetoacetate to produce tetraketones (eq. 2) (25). This could involve

[2] 

either a direct condensation of the dianion with a monoanion or elimination of ethoxide from the keto ester monoanion and condensation of the resulting acylketene with the dianion.

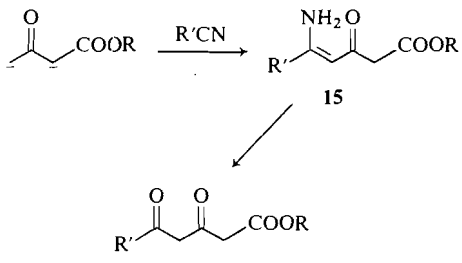
We have found that a similar acylation of methyl acetoacetate may be achieved. If, in generation of the dianion of methyl acetoacetate, only ½ equiv. of *n*-butyllithium is added and the reaction left at room temperature for a considerable time (5 days) before quenching, the methyl acetoacetate undergoes self-condensation and methyl orsellinate (**13**) is obtained (eq. 3). The

[3] 

reaction time may be shortened considerably by raising the reaction temperature but as yet the maximum yield obtained is only 23%. It was also possible to isolate the intermediate triketo ester **14** by quenching the reaction carefully with a phosphate buffer (p*H* 6.5). The triketo ester **14** was characterized by its spectral properties but this compound was not sufficiently stable for elemental analysis. This material underwent spontaneous conversion to methyl orsellinate (**13**) on standing at 0 °C for 12 h. The triketo ester **14** has been synthesized via the carboxylation of the trianion of diacetylacetone and the cyclization of **14** to **13** was also reported in this work (26).

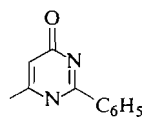
The n.m.r. spectra of all the acylated β-keto esters indicated that they existed, in solution at least, with the β-diketone mainly in the enol form. The n.m.r. spectra, or other spectroscopic data, did not permit a clear decision to be made as to which enol, or enols, are formed.

The reaction of dianion **10** with a nitrile also offers the possibility of adding an acyl group to the keto ester (eq. 4).



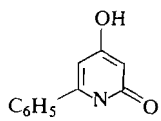
[4]

Recently it has been reported that ethyl acetoacetate may be condensed with benzonitrile using 2 equiv. of sodium amide to give the enamine **15** ($R' = C_6H_5$; R = Et) but the reaction is complicated by nucleophilic attack of the amide ion on the nitrile and subsequent condensation of the benzamidine with the keto ester to give the pyrimidone **16**.



16

We found that the reaction between dianion **10** and benzonitrile was sluggish and extended reaction times were necessary to produce reasonable amounts of product. After 12 h at room temperature methyl 5-amino-3-oxo-5-phenylpent-4-enoate (**15**, $R' = C_6H_5$; R = Me) was isolated in good yield (66%) along with some (29%) hydroxypyridone **17**, which arises from cyclization of **15** ($R' = C_6H_5$; R = Me). In



17

fact, this cyclization occurred in quantitative yield on attempted distillation of **15** ($R' = C_6H_5$; R = Me) and provides a ready route to **17**. Extension of this reaction to the condensation of acetonitrile with dianion **10** gave the enamine **15** (R′ = R = Me) in high yield and no evidence for the formation of the corresponding hydroxypyridone was observed. In fact this enamine (**15**, R′ = R = Me) appears to be quite stable to thermolysis and under a variety of conditions **15** (R′ = R = Me) sublimed unchanged.

The synthesis of the esters of 3,5-dioxohexanoic acid has been reported as early as 1906 (27*a*) and more recently in the photolysis of triacetic acid lactone (27*b*). However, the above acylation of the dianion of β-keto esters offers a new route to a wide range of β,δ-diketo esters which now can be prepared in reasonable yield. These intermediates may undergo further reactions and their chemistry awaits additional exploitation. The dianion of β-keto esters also undergoes condensation with nitriles to give the enamines **15** which may, in the case of $R' = C_6H_5$, be cyclized to the hydroxypyridone **17**.

Experimental

All melting points, which were recorded on a Kofler micro hot stage, and boiling points are uncorrected and are reported in °C. The i.r. spectra were recorded on a Perkin–Elmer Model 700 spectrometer and were calibrated with the 1601 cm^{-1} band of polystyrene. The u.v. spectra were recorded on a Unicam Model SP 800 or a Cary Model 14 spectrophotometer. The proton nuclear magnetic resonance spectra were recorded on either a Varian T-60 or HA-100 spectrometer and the chemical shifts are reported in δ units from internal tetramethylsilane. Low resolution mass spectra were recorded on an AEI MS-9 or an Atlas CH-4b mass spectrometer, and the high resolution spectra were recorded on the MS-9 spectrometer. Both instruments were operated at an ionizing potential of 70 eV. Vapor phase chromatograms were obtained on a Varian-Aerograph Model 90 P3 chromatograph using a 5 ft × ¼ in. column of 5% QF-1 on 60–80 mesh Chromosorb W.

The support used for all micro thin-layer and preparative thin-layer chromatography was silica gel PF_{254} (Merck). Merck silica <0.03 mm or finer than 200 mesh was used for column chromatography. Microanalyses were performed by Mr. Peter Borda, University of British Columbia, Vancouver.

All solvents were dried and distilled immediately before use. All reactions were run under an atmosphere of nitrogen or argon. Commerical sodium hydride (50–57% mineral oil) was used without prior washing to remove the mineral oil. Commercial solutions of *n*-butyllithium in hexane were used directly and were standardized by double titration (28) or direct titration (29).

Methyl 3,5-Dioxohexanoate (11, R = Me)

Sodium hydride (0.467 g, 11.0 mmol), as a 57% mineral oil dispersion, was weighed into a 50 ml oven-dried flask and tetrahydrofuran (*ca.* 25 ml) was distilled directly into this flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmol) was added dropwise to the cooled slurry and the reaction allowed to stir for 10 min after the addition was complete. *n*-Butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, was added dropwise to the reaction and after 10 min the first portion of methyl acetate (0.372 g, 5.0 mmol) was added. After a further 15 min, additional *n*-butyllithium (5 ml, 10.5 mmol) was added very slowly. A further period of 15 min was allowed to elapse before the second portion of methyl acetate (0.371 g, 5.0 mmol) was added and the reaction stirred for a final 15 min

before being quenched with concentrated hydrochloric acid (3 ml). The reaction was worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium hydrogen carbonate solution (2 × 10 ml) and with saturated sodium chloride solution (4 × 15 ml), dried over anhydrous sodium sulfate and filtered. The solvents were removed under reduced pressure and the resulting yellow oil distilled under vacuum to give 1.120 g (71%) of **11** (R = Me); b.p. 44–46 °C (0.3 mm), (lit. (27*b*) b.p. 65°/11 mm); i.r. ($CHCl_3$) 3450, 1740, and 1600 cm^{-1}; n.m.r. ($CDCl_3$) δ 14.2 (broad s, exchangeable D_2O, 1H), 5.62 (s, 0.67H), 3.79 (s, 3H), 3.57 (s, 0.64H), 3.35 (s, 2H), 2.27 (s, 0.95 H), and 2.10 p.p.m. (s, 2.13H), 68% enol; mass spectrum, *m/e* (relative intensity) 158(6), 127(6), 126(8), 116(8), 107(8), 101(6), 98(9), 91(9), 85(43), 77(6), 69(21), 59(10) and 43(100).

Anal. Calcd. for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 53.14; H, 6.26.

*Methyl 3,5-Dioxooctanoate (**11**, R = n-Pr)*

This compound was prepared by the same procedure as that employed in the preparation of methyl 3,5-dioxohexanoate (**11**, R = Me). The reagents used in the preparation were sodium hydride (0.465 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), two portions of *n*-butyllithium (4.6 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, which gave 1.250 g (67%) of **11** (R = *n*-Pr), b.p. 83–85 °C (0.1 mm); i.r. (CCl_4) 3500, 1740, and 1595 cm^{-1}; n.m.r. (CCl_4) δ 14.3 (broad s, 0.97H), 5.52 (s, 0.98H), 3.66 (s, 3H), 3.20 (s, 1.96H), 2.26 (t, J = 7 Hz, 2.0H), 1.66 (m, 2.0H) and 0.96 p.p.m. (t, J = 7 Hz, 3.0H), 97% enol; mass spectrum, *m/e* (relative intensity) 186(41), 172(22), 158(68), 157(57), 143(81), 126(73), 115(62), 113(92), 101(100), 97(28), 85(73), 84(72), 71(90), 69(51), 59(81), and 43(17).

Anal. Calcd. for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.35; H, 7.47.

*Condensation of Ethyl Butanoate with Dianion **10***

This reaction was performed in a similar manner to that in which methyl 3,5-dioxohexanoate was prepared. The reagents used were sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.61 g, 10.0 mmol), two portions of *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, and two portions of ethyl butanoate (0.582 g, 5.0 mmol), which gave 1.441 g of a pale yellow oil. Vapor phase chromatographic analysis (140 °C) of this oil showed it to contain two components. Distillation through a short Vigreux column gave partial separation of these components and repeated distillation (three more times), although accompanied by considerable resinification of the oil, gave the pure components identified as methyl 3,5-dioxooctanoate (**11**, R = *n*-Pr) (0.619 g, 33%) by comparison of i.r. and n.m.r. spectra with those of **11** (R = *n*-Pr) prepared above, and ethyl 3,5-dioxooctanoate (0.223 g, 11%), b.p. 94–96 °C (0.1 mm); i.r. (CCl_4) 3500, 1740, and 1600 cm^{-1}; n.m.r. (CCl_4) δ 14.6 (broad s, exchangeable D_2O, 1H), 5.57 (s, 1H), 4.13 (q, J = 7 Hz, 2H), 3.08 (s, 2H), 2.27 (t, J = 7 Hz, 2H), 1.65 (m, 2H), 1.27 (t, J = 7 Hz, 2H) and 0.95 p.p.m. (t, J = 7 Hz, 3H); mass spectrum, *m/e* (relative intensity) 200(20), 156(47), 143(78), 126(70), 115(64), 113(80), 101(100), 97(30), 85(74), 84(70), 71(85), 69(15), 59(60), and 43(28).

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 59.98; H, 8.08.

*Methyl 3,5-Dioxopentanoate (**11**, R = H)*

This compound was prepared by the same procedure as that employed in the preparation of methyl 3,5-dioxohexanoate (**11**, R = Me). The reagents used in the preparation were sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.160 g, 10.0 mmol), two portions of *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, and two portions of methyl formate (0.300 g, 5.0 mmol), which gave 0.993 g (69%) of **11** (R = H) b.p. 55–56 °C (0.1 mm); i.r. (CCl_4) 3500, 1740, 1640, and 1590 cm^{-1}; n.m.r. (CCl_4) δ 13.5 (broad s, exchangeable D_2O, 1H), 7.72 (d, J = 5 Hz, 1H), 5.63 (d, J = 5 Hz, 1H), 3.72 (s, 3H), and 3.32 p.p.m. (s, 2H); mass spectrum, *m/e* (*a*) high resolution calcd. for $C_6H_8O_4$: 144.0422 a.m.u.; found: 144.0421 a.m.u.; (*b*) *m/e* (relative intensity) 144(5), 131(3), 127(2), 126(11), 113(15), 112(17), 101(100), 97(30), 85(67), 71(63), 59(43), and 43(28).

*Condensation of Methyl Benzoate with Dianion **10***

Sodium hydride (0.468 g, 11.0 mmol), as a 57% mineral oil dispersion, was weighed into a 50 ml oven dried flask and tetrahydrofuran (*ca.* 25 ml) was distilled directly into this flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. Methyl acetoacetate (1.164 g, 10.0 mmol) was added dropwise to the cooled slurry and after the addition was complete the reaction was allowed to stir for 10 min. *n*-Butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, was added dropwise to the reaction and after 10 min the first portion of methyl benzoate (0.680 g, 5.0 mmol) was added. After a further 15 min additional *n*-butyllithium (5 ml, 10.5 mmol) was added very slowly. A further period of 15 min was allowed to elapse before the second portion of methyl benzoate (0.680 g, 5.0 mmol) was added and the reaction was stirred for a final 15 min before being quenched with concentrated hydrochloric acid (3 ml). The reaction was worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium hydrogen carbonate solution (4 × 15 ml) and with saturated sodium chloride solution (2 × 15 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed under reduced pressure and the resulting red oil distilled under vacuum to give 0.817 g (37%) of methyl 3,5-dioxo-5-phenylpentanoate (**11**, R = C_6H_5), b.p. 127–129 °C (0.1 mm); i.r. (CCl_4) 3450, 1740, and 1600 cm^{-1}; u.v. (CH_3OH) 322 nm (1.3×10^3); n.m.r. (CCl_4) δ 14.3 (broad s, exchangeable D_2O, 1H), 7.87 (m, 2H), 7.37 (m, 3H), 6.26 (s, 1H), 3.70 (s, 3H), and 3.38 p.p.m. (s, 2H); mass spectrum, *m/e* (relative intensity) 220 (21), 205(11), 203(34), 189(26), 188(65), 174(16), 173(11), 163(57), 161(58), 147(74), 105(100), 85(15), 77(48), 69(51), 51(37), and 43(28).

Anal. Calcd. for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.42; H, 5.65.

The basic aqueous extract (saturated sodium hydrogen carbonate washings) was acidified to p*H* 2 by addition of

1 *M* hydrochloric acid and the resulting solution extracted with ether (3 × 35 ml); these ethereal extracts were combined, washed with saturated sodium chloride solution (3 × 15 ml), dried over sodium sulfate, and filtered. The solvents were removed under reduced pressure and the resulting solid recrystallized from a mixture of hexane and ether to give 0.684 g (30%) of 3,5-dioxo-5-phenylpentanoic acid (**12**, Ar = C_6H_5), m.p. 93–97 °C (lit. (20) m.p. 94–96 °C).

*Condensation of Methyl 4-Methoxybenzoate with Dianion **10***

This reaction was performed in a similar manner to the condensation of methyl benzoate with dianion **10** above. The reagents used were sodium hydride (0.467 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.161 g, 10.0 mmol), two portions of *n*-butyllithium (4.5 ml, 10.6 mmol), as a 2.35 *M* solution in hexane, and two portions of methyl 4-methoxybenzoate (0.831 g, 5.0 mmol), which gave 0.741 g (29%) of 5-(4-methoxyphenyl)-3,5-dioxopentanoic acid (**12**, Ar = *p*-MeO—C_6H_4) as colorless needles (from hexane–ether), m.p. 103–105 °C, and 1.051 g (42%) of methyl 5-(4-methoxyphenyl)-3,5-dioxopentanoate (**11**, R = *p*-MeO—C_6H_4), b.p. 142–143 °C (0.1 mm). These compounds were characterized as follows.

(*a*) 5-(4-Methoxyphenyl)-3,5-dioxopentanoic acid (**12**, Ar = *p*-MeO—C_6H_4); i.r. ($CHCl_3$) 3700, 3500, 1720, and 1600 cm^{-1}; u.v. (CH_3OH) 326 (7.1 × 10) and 287 nm (shoulder, 4.4 × 10^3); n.m.r. (CD_3COCD_3) δ 14.6 (broad s, exchangeable D_2O, 1H), 11.2 (broad s, exchangeable D_2O, 1H), 7.87 (m, 2H), 6.93 (m, 2H), 3.90 (s, 3H) and 3.37 p.p.m. (s, 2H); mass spectrum, *m/e* (relative intensity) 237(5), 236(43), 219(5), 218(42), 193(43), 192(96), 191(67), 178(50), 177(84), 161(68), 149(20), 136(57), 135(100), 121(21), 109(75), 108(57), 105(15), 92(32), 85(30), 77(37), 69(45), 51(35), 44(40), and 43(35).

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.02; H, 5.12. Found: C, 61.08; H, 5.26.

(*b*) Methyl 5-(4-Methoxyphenyl)-3,5-dioxpentanoate (**11**, R = *p*-MeO—C_6H_4); i.r. (CCl_4) 3500, 1740, and 1600 cm^{-1}; u.v. (CH_3OH) 325 (5.4 × 10) and 285 nm (shoulder, 2.0 × 10^3); n.m.r. (CCl_4) δ 14.3 (broad s, exchangeable D_2O, 1H), 7.85 (m, 2H), 6.90 (m, 2H), 6.20 (s, 1H), 3.90 (s, 3H), 3.77 (s, 3H), and 3.47 p.p.m. (s, 2H); mass spectrum, *m/e* (relative intensity) 250(21), 217(57), 190(44), 177(65), 135(100), 109(23), 108(13), 107(15), 105(16), 104(32), 91(29), 77(29), 69(65), 59(23), and 43(55).

Anal. Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.43; H, 5.72.

Base Dependency Study

(a) Lithium Diisopropylamide

(i) Attempted acylation with methyl acetate. Diisopropylamine (1.536 g, 15.0 mmol) was weighed into an oven-dried flask and tetrahydrofuran (*ca.* 25 ml) was distilled directly into this flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. *n*-Butyllithium (7.5 ml, 15.8 mmol), as a 2.1 *M* solution in hexane, was added dropwise to the cooled solution and the reaction allowed to stand for 10 min after the addition was complete. Methyl acetoacetate (0.580 g, 5.0 mmol) was added to the reaction over a period of about 10 min and a further period of 10 min allowed to elapse before methyl acetate (0.370 g, 5.0 mmol) was added. After 10 min the reaction was quenched with concentrated hydrochloric acid (*ca.* 4 ml) and the reaction worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with water (3 × 20 ml) and with saturated sodium chloride solution (2 × 20 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed at reduced pressure to give 0.601 g of pale yellow oil. Vapor phase chromatography analysis of this oil (120 °C) showed it to be methyl acetoacetate contaminated with minor amounts of diisopropylamine and methyl acetate. Both v.p.c. and t.l.c. analysis of this oil and the acidified crude reaction mixture failed to indicate any of the desired product, methyl 3,5-dioxohexanoate (**11**, R = Me). Distillation of the oil at reduced pressure gave 0.521 g (90%) of methyl acetoacetate, b.p. 51–52 °C (17 mm) identified by v.p.c. analysis and comparison of its i.r. and n.m.r. spectra with those of authentic material.

(ii) Attempted acylation with methyl benzoate. This reaction was run as above using 0.680 g (5.0 mmol) methyl benzoate to give 0.924 g (91%) of *N,N*-diisopropylbenzamide m.p. 68–69 °C (lit. (30) m.p. 69–71 °C); i.r. ($CHCl_3$) 1620 cm^{-1}; n.m.r. ($CDCl_3$) δ 7.30 (s, 5H), 3.67 (septuplet, J = 6 Hz, 2H) and 1.32 p.p.m. (d, J = 6 Hz, 12H); v.p.c. and t.l.c. analysis of the crude oil failed to show any of the desired products methyl 3,5-dioxo-5-phenylpentanoate (**11**, R = C_6H_5) or 3,5-dioxo-5-phenylpentanoic acid (**12**, Ar = C_6H_5).

(b) Lithium N-Cyclohexyl-N-isopropylamide

(i) Acylation with methyl acetate. *N*-Cyclohexyl-*N*-isopropylamine, which had been distilled from calcium hydride and stored over potassium hydroxide until used, was used in place of diisopropylamine above to give 0.537 g of a yellow oil. Vapor phase chromatography analysis of this oil (120 °C) showed it to contain methyl acetoacetate and methyl 3,5-dioxohexanoate (**11**, R = Me) in the ratio 93:7. Distillation of the oil at reduced pressure gave 0.486 g (88%) of methyl acetoacetate, b.p. 49–52 °C (17 mm), identified by comparison of i.r. and n.m.r. spectra with those of authentic material, and 40 mg of residue. The residue was distilled in a bulb-to-bulb distillation apparatus (bath temperature 50 °C) under vacuum (0.2 mm) to give 37 mg (4%) of methyl 3,5-dioxohexanoate (**11**, R = Me) which was identified by comparison with previously prepared material by v.p.c. (120 °C) and t.l.c.

(ii) Acylation with methyl benzoate. This reaction was run as above using methyl benzoate (5.0 mmol) to give a yellow semicrystalline material. Recrystallization from ether gave 1.080 g (88%) of *N*-cyclohexyl-*N*-isopropylbenzamide, m.p. 76–78 °C; i.r. ($CHCl_3$) 1620 cm^{-1}; n.m.r. (CCl_4) δ 7.30 (s, 5H), 3.87–3.00 (m, 2H), 2.20–1.00 (m, 10H), and 1.30 p.p.m. (d, J = 6 Hz, 6H); mass spectrum, *m/e* (relative intensity) 246(22), 245(37), 244(14), 230(22), 203(27), 202(46), 189(15), 188(39), 165(11), 164(37), 163(54), 162(62), 149(11), 148(41),

146(23), 145(32), 129(19), 128(19), 118(36), 117(41), 115(33), 105(72), 103(35), 85(33), 79(35), 78(44), 76(93), 56(83), and 54(100).

The mother liquors from the recrystallization were found by v.p.c. analysis (200 °C) to contain methyl 3,5-dioxo-5-phenylpentanoate and were subjected to chromatography on silica gel, using chloroform as eluent. The major component isolated from this chromatography was methyl 3,5-dioxo-5-phenylpentanoate (**11**, R = C_6H_5) (0.085 g, 8%), identified by comparison of its i.r. spectrum with that of previously prepared material.

*Condensation of the Monoanion of Methyl Acetoacetate with Dianion **10***

(a) At Room Temperature, Acid Quenching

Sodium hydride (0.466 g, 11.0 mmol), as a 57% mineral oil dispersion, was weighed into an oven-dried flask and freed from mineral oil by washing with hexane (*ca.* 15 ml) and decantation. The washing procedure was repeated twice with hexane and the residual hexane was removed by washing with tetrahydrofuran. After decantation of the tetrahydrofuran, fresh tetrahydrofuran was distilled directly into the flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. Methyl acetoacetate (1.162 g, 10.0 mmol) was added dropwise to the cooled slurry and after the addition was complete the reaction was allowed to stand for a period of about 10 min. *n*-Butyllithium (2.2 ml, 5.1 mmol), as a 2.3 *M* solution in hexane, was added dropwise to the reaction which was then allowed to warm to room temperature. After a period of 24 h the reaction was quenched by addition of concentrated hydrochloric acid (*ca.* 1.5 ml) and worked up by addition of ether (35 ml) and water (5 ml). The aqueous phase, the p*H* of which was *ca.* 2, was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 × 20 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed under reduced pressure to give 0.983 g of brown oil. Distillation of this oil at reduced pressure gave 0.716 g (62%) of methyl acetoacetate, b.p. 45–47 °C (14 nm), identified by comparison of its i.r. and n.m.r. spectra with those of authentic material, and a brown solid residue which was crystallized from methanol to give 0.220 g (24%) of methyl orsellinate (**13**), m.p. 138–140 °C (lit. (31) m.p. 138–139 °C), mixture m.p. 138–140 °C.

(b) At Room Temperature, Buffered Quenching

This reaction was performed in the same manner as the preceding reaction. The reagents employed were sodium hydride (0.463 g, 11.0 mmol), as a 57% mineral oil dispersion, methyl acetoacetate (1.160 g, 10.0 mmol), and *n*-butyllithium (2.5 ml, 5.2 mmol), as a 2.1 *M* solution in hexane. After the 24 h reaction period, the reaction was quenched by adding it, via a stainless steel cannula, to a vigorously stirred mixture of ether (50 ml) and buffer solution (prepared by dissolving sodium dihydrogen orthophosphate (4 g) and disodium hydrogen orthophosphate (4 g) in water (20 ml)). The aqueous phase was separated, saturated with sodium chloride, and further extracted with ether (3 × 20 ml). The ethereal layers were combined, washed with saturated sodium chloride solution (20 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed under reduced pressure and the resulting oil chromatographed on silica gel, using a mixture of benzene and ethyl acetate (1:1 v/v) as eluent. Three components were obtained from the chromatography, and these, in order of their elution, were methyl 3,5,7-trioxooctanoate (**14**) (83 mg, 8%), as a pale yellow, unstable oil, which on standing overnight at 0 °C was converted to methyl orsellinate in quantitative yield, methyl orsellinate (**13**) (155 mg, 17%) as cream colored needles, m.p. 138–140 °C; and methyl acetoacetate (0.679 g, 59%). Methyl 3,5,7-trioxooctanoate was characterized by; i.r. ($CHCl_3$) 3400, 1740, 1720, 1640, 1620 and 1600 cm^{-1}; n.m.r. (CCl_4) δ 14.60 (broad s, exchangeable D_2O, 1H), 6.20 (m, 1H), 3.96 (s, 3H), 3.70 (s, 2H), 3.67 (s, 2H) and 2.43 p.p.m. (s, 3H); mass spectrum, *m/e* (relative intensity) 184(9), 182(4), 151(4), 150(13), 143(7), 142(26), 127(40), 117(9), 113(27), 101(9), 100(24), 85(100), 73(21), 69(20), 61(34), and 43(100).

(c) At Reflux Temperature

Reaction mixture obtained similarly to *b* was allowed to warm to room temperature. The flask was then transferred to a glove bag where, under an atmosphere of nitrogen, the septum cap was removed and replaced with a reflux condenser, the top of which was stoppered with a fresh septum cap and heated under nitrogen until a moderate rate of reflux was obtained. After 2 h at reflux temperature,the heating was discontinued and the flask cooled in ice to 0 °C. The reaction was quenched with concentrated hydrochloric acid (*ca.* 1.5 ml) and worked up by the addition of ether (35 ml) and water (5 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 × 20 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed under reduced pressure and distillation of the resulting oil at reduced pressure gave 0.821 g (71%) of methyl acetoacetate, b.p. 46–48 °C (14 mm), identified by comparison of its i.r. spectrum with that of authentic material, and a brown residue, which on titration with methanol gave 0.213 g (23%) of methyl orsellinate (**13**), as pale yellow needles, identified by comparison of its i.r. spectrum with that of authentic material.

*Condensation of Benzonitrile with Dianion **10***

Sodium hydride (0.467 g, 11.0 mmol), as a 57% mineral oil dispersion, was weighed into a 50 ml oven-dried flask and tetrahydrofuran (*ca.* 25 ml) was distilled directly into this flask from lithium aluminum hydride. The flask was equipped with a magnetic stirrer, stoppered (septum cap), cooled in ice, and flushed with nitrogen. Methyl acetoacetate (1.160 g, 10.0 mmol) was added dropwise to the cooled slurry and the reaction allowed to stir for 10 min after the addition was complete. *n*-Butyllithium (5 ml, 10.5 mmol), as a 2.1 *M* solution in hexane, was added dropwise to the reaction and after 10 min benzonitrile (1.031 g, 10.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked up by the addition of ether (35 ml) and water (10 ml) and the resulting precipitate filtered off. The precipitate was

washed with acetone (2 × 10 ml), air dried, and sublimed at 150 °C (0.2 mm) to give 0.547 g (29%) of 4-hydroxy-6-phenylpyridone (**17**) as colorless spars, m.p. 314–316 °C (lit. (32) m.p. 315–318 °C); i.r. (KBr disc) 1640, 1620, 1595, and 1560 cm^{-1}; u.v. (C_2H_5OH) 310 and 255 nm, (C_2H_5OH + NaOH) 240 nm; mass spectrum, *m/e* (relative intensity) 188(16), 187(100), 186(17), 160(6), 159(15), 158(10), 147(11), 146(6), 130(19), 104(33), 103(33), 91(14), 77(21), 69(9), and 51(15).

The aqueous phase of the filtrate was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (6 × 15 ml), dried over anhydrous sodium sulfate, and filtered. The solvents were removed under reduced pressure and the resulting oil chromatographed on silica gel using ethyl acetate as eluent. The major fraction from this chromatography was collected, and freed from eluent by distillation at room temperature under reduced pressure to give 1.466 g (66%) of methyl 5-amino-3-oxo-5-phenyl-pent-4-enoate (**15**, R = Me; R′ = C_6H_5) as a pale yellow oil; i.r. ($CHCl_3$) 3550, 1740, 1615, and 1600 cm^{-1}; u.v. (C_2H_5OH) 325 nm; n.m.r. (CCl_4) δ 8.00 (broad s, exchangeable D_2O, 1H), 7.41 (m, 5H), 6.20 (broad s, exchangeable D_2O, 1H), 5.37 (s, 1H), 3.60 (s, 3H), and 3.27 p.p.m. (s, 2H); mass spectrum (*a*) high resolution calcd. for $C_{12}H_{13}NO_3$: 219.0895 a.m.u.; found: 219.0896 a.m.u.; (*b*) low resolution *m/e* (relative intensity) 219(26), 159(15), 146(47), 127(35), 121(32), 119(95), 118(95), 103(30), 84(52), 82(22), 59(46), and 43(100).

*Thermolysis of Methyl 5-Amino-3-oxo-5-phenylpent-4-enoate (**15**, R = Me; R′ = C_6H_5)*

Enamine **15** (R = Me; R′ = C_6H_5) (156 mg, 0.71 mmol) was placed in a bulb-to-bulb distillation apparatus and heated to 150 °C under reduced pressure (0.2 mm). After ½ h the starting material had completely disappeared and white spars had been deposited on the cooler parts of the apparatus. These crystals were collected and found to amount to 134 mg (100%) of 4-hydroxy-6-phenylpyridone (**17**), which exhibited identical m.p., and i.r. and u.v. spectra to that obtained previously.

*Methyl 5-Amino-3-oxohex-4-enoate (**15**, R = R′ = Me)*

Reaction was run as above using sodium hydride (0.467 g, 11.0 mmol), methyl acetoacetate (1.160 g, 10.0 mmol), *n*-butyllithium (5 ml of 2.1 *M*, 10.5 mmol), and acetonitrile (0.409 g, 10.0 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h before being quenched with concentrated hydrochloric acid (2 ml). The reaction was worked up by the addition of ether (35 ml) and water (10 ml). The aqueous phase was separated and further extracted with ether (2 × 35 ml). The ethereal extracts were combined, washed with saturated sodium chloride solution (4 × 15 ml), dried over anhydrous magnesium sulfate, and filtered. The solvents were removed under reduced pressure. The resulting semi-solid was crystallized from chloroform to give 1.490 g (86%) of **15** (R = R′ = Me) as long yellow needles, m.p. 103–104 °C. Sublimation at 175 °C (0.2 mm) gave colorless spars but did not raise the melting point; i.r. ($CHCl_3$) 3550, 1740, 1625, and 1610 cm^{-1}; u.v. (CH_3OH) 303 nm (16.8×10^3) and (CH_3OH + NaOH) 274 nm; n.m.r. ($CDCl_3$) δ 10.0 (broad s, exchangeable D_2O, 1H), 5.10 (s, 1H), 3.70 (s, 3H), 3.33 (s, 2H), and 1.97 p.p.m. (s, 3H); mass spectrum, *m/e* (relative intensity) 158(3), 157(26), 126(2), 125(3), 85(7), 84(100), 83(2), 70(2), 68(2), 54(2), 43(3), 42(5) and 41(4).

Anal. Calcd. for $C_7H_{11}O_3N$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.18; H, 6.99; N, 8.84.

We are grateful to the University of British Columbia and the National Research Council of Canada for support of this work.

1. C. R. HAUSER and T. M. HARRIS. J. Am. Chem. Soc. **80**, 6360 (1958).
2. S. D. WORK and C. R. HAUSER. J. Org. Chem. **28**, 725 (1963).
3. R. J. LIGHT and C. R. HAUSER. J. Org. Chem. **25**, 538 (1960).
4. F. B. KIRBY, T. M. HARRIS, and C. R. HAUSER. J. Org. Chem. **28**, 2266 (1963).
5. M. L. MILES, T. M. HARRIS, and C. R. HAUSER. J. Org. Chem. **30**, 1007 (1965).
6. T. M. HARRIS and R. L. CARNEY. J. Am. Chem. Soc. **89**, 6734 (1967).
7. K. G. HAMPTON, T. M. HARRIS, C. M. HARRIS, and C. R. HAUSER. J. Org. Chem. **30**, 4263 (1965).
8. T. M. HARRIS, S. BOATMAN, and C. R. HAUSER. J. Am. Chem. Soc. **87**, 3186 (1965).
9. T. M. HARRIS and G. P. MURPHY. J. Am. Chem. Soc. **93**, 6708 (1971).
10. A. J. BIRCH and F. W. DONOVAN. Aust. J. Chem. **6**, 360 (1953).
11. (*a*) J. H. RICHARDS and J. B. HENDRICKSON. The biosynthesis of steroids, terpenes, and acetogenins. W. A. Benjamin, New York, N.Y. 1964; (*b*) J. D. BU'LOCK. The biosynthesis of natural products. McGraw-Hill, London. 1965.
12. J. N. COLLIE. J. Chem. Soc. **91**, 1806 (1907).
13. A. J. BIRCH, D. W. CAMERON, and R. W. RICHARDS. J. Chem. Soc. 4395 (1960).
14. J. R. BETHEL and P. MAITLAND. J. Chem. Soc. 3751 (1960).
15. T. MONEY, F. W. COMER, G. R. WEBSTER, I. G. WRIGHT, and A. I. SCOTT. Tetrahedron, **23**, 3435 (1967).
16. J. L. DOUGLAS and T. MONEY. Can. J. Chem. **45**, 1990 (1967).
17. J. L. DOUGLAS and T. MONEY. Tetrahedron, **23**, 3545 (1967).
18. T. MONEY. Chem. Rev. **70**, 553 (1970).
19. S. N. HUCKIN and L. WEILER. Tetrahedron Lett. 2405 (1972).
20. J. F. WOLFE, T. M. HARRIS, and C. R. HAUSER. J. Org. Chem. **29**, 3249 (1964).
21. (*a*) L. WEILER. J. Am. Chem. Soc. **92**, 6702 (1970); (*b*) S. N. HUCKIN and L. WEILER. J. Am. Chem. Soc. In press; (*c*) S. N. HUCKIN Ph.D. Thesis, University of British Columbia, Vancouver, British Columbia, 1973.
22. S. N. HUCKIN and L. WEILER. Tetrahedron Lett. 4835 (1971).
23. (*a*) K. W. YANG, J. G. CANNON, and J. G. ROSE. Tetrahedron Lett. 1791 (1970); (*b*) B. SINGH. Tetrahedron Lett. 321 (1971).

24. R. A. OLOFSON and C. M. DOUGHERTY. J. Am. Chem. Soc. **95**, 579, 582 (1973).
25. T. P. MURRAY and T. M. HARRIS. J. Am. Chem. Soc. **94**, 8253 (1972).
26. T. T. HOWARTH, G. P. MURPHY, and T. M. HARRIS. J. Am. Chem. Soc. **91**, 517 (1969).
27. (*a*) F. SPROXTON. J. Chem. Soc. **89**, 1186 (1906); (*b*) C. T. BEDFORD, J. M. FORRESTER, and T. MONEY. Can. J. Chem. **48**, 2645 (1970).
28. R. R. TURNER, A. G. ALTENEAU, and T. C. CHENG. Anal. Chem. **42**, 1835 (1970).
29. S. C. WATSON and J. F. EASTHAM. J. Organomet. Chem. **9**, 165 (1967).
30. B. PRAJSNAR and C. TROSZKIEWICZ. Rocz. Chem. **36**, 1029 (1968).
31. A. HESSE. J. Prakt. Chem. **57**, 268 (1852).
32. F. ARNDT, B. EISERT, H. SCHLOZ, and E. ARON. Chem. Ber. **69**, 2373 (1936).