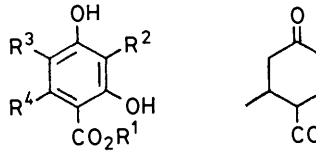
Convenient Syntheses of Alkyl β-Resorcylate Derivatives

By **Anthony G. M. Barrett** * and **Timothy M. Morris**, Department of Chemistry, Imperial College, London SW7 2AY
Derek H. R. Barton, Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

Syntheses of methyl 2,4-dihydroxy-6-methyl- (1a) and -3,6-dimethylbenzoates (1b) and methyl 2,4-dihydroxy-6-pentylbenzoate (1c) are described. Condensation reactions of dimethyl sodiomalonate with the dianion derived from pentane-2,4-dione or the dimerisation of the methyl acetoacetate dianion or the acetylation of the trianion derived from methyl 3,5,7-trioxo-octanoate gave (1a) (≤78%) after work-up at pH 9. Analogous convenient, short, optimised syntheses of (1b and c) are given in detail.

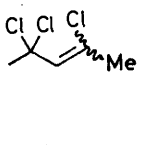
METHYL 2,4-dihydroxy-6-methyl- (1a) (methyl orsellinate) and -3,6-dimethyl-benzoate (methyl β-orsinolcarboxylate) (1b) and methyl 2,4-dihydroxy-6-pentylbenzoate (1c) (methyl olivetolcarboxylate) are major odoriferous components of oakmoss (*Evernia prunastri*). General short syntheses of these and related alkyl β-resorcylate derivatives are desirable. Existing methods proceed *via* the oxidation of alkyl 6-alkyl- (or 3,6-dialkyl-) 2,4-dioxocyclohexanecarboxylates [*e.g.* (2)] using diverse halogenating reagents,[1-3] or sulphuric acid in acetic anhydride [4] or *via* catalytic dehydrogenation.[5] For example, condensation of methyl crotonate with methyl acetoacetate gave methyl 6-methyl-2,4-dioxocyclohexanecarboxylate (2) (67%).[2,3] Subsequent bromination [3] (3 equiv.) gave methyl 3,5-dibromo-2,4-dihydroxy-6-methylbenzoate (1d) (95%) which gave methyl orsellinate (1a) (90%) on Santesson's debromination.[6] Alternatively, oxidation of dione (2) with sulphuric acid in acetic anhydride and acetic acid was said to give on subsequent alcoholysis methyl orsellinate (1a) (96%).[4]



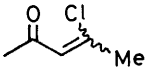
(1)

a; $R^1 = R^4 = Me, R^2 = R^3 = H$
b; $R^1 = R^2 = R^4 = Me, R^3 = H$
c; $R^1 = Me, R^2 = R^3 = H, R^4 = n\text{-}C_5H_{11}$
d; $R^1 = R^4 = Me, R^2 = R^3 = Br$
e; $R^1 = Et, R^2 = R^3 = H, R^4 = Me$
f; $R^1 = Bu^n, R^2 = R^4 = Me, R^3 = H$

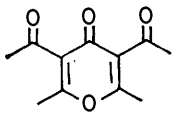
(2)



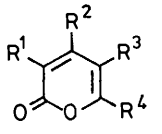
(3)



(4)
a; *E*
b; *Z*



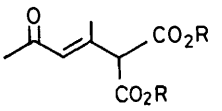
(5)



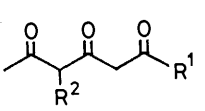
(6)

a; $R^1 = CO_2Me, R^2 = R^4 = Me, R^3 = H$
b; $R^1 = R^3 = H, R^2 = R^4 = Me$
c; $R^1 = H, R^2 = OH, R^3 = R^4 = Me$

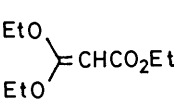
As an alternative, we considered that the condensation of dimethyl malonate with pentane-2,4-dione should provide methyl orsellinate (1a) directly and thus avoid the oxidation step which is often unsatisfactory.[1] This has analogy in the reported [7] condensation of 3-acetoxyhex-2-en-4-one with dimethyl malonate giving methyl β-orsinolcarboxylate (1b) directly. Pentane-2,4-dione was converted into trichloride (3) with phosphorus pentachloride. This on hydrolysis with calcium carbonate gave (*E*/*Z*)-4-chloropent-3-en-2-one (4) [8] (67%). Dichlorotriphenylphosphorane, triphenylphosphine–carbon tetrachloride,[9] or oxalyl chloride [10] were alternative, but less convenient and/or expensive chlorinating reagents.



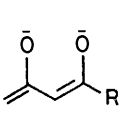
(7)
a; R = Me
b; R = Et



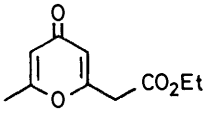
(8)
a; $R^1 = CH_2CO_2Me, R^2 = H$
b; $R^1 = CH{=}C(OEt)_2, R^2 = H$
c; $R^1 = EtO, R^2 = H$
d; $R^1 = MeO, R^2 = H$
e; $R^1 = MeO, R^2 = Me$



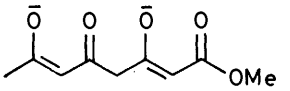
(9)



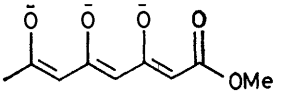
(10)
a; R = Me
b; R = OMe
c; R = OEt
d; R = CH=C(OMe)–O



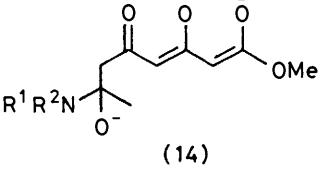
(11)



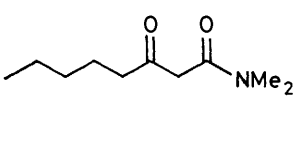
(12)



(13)



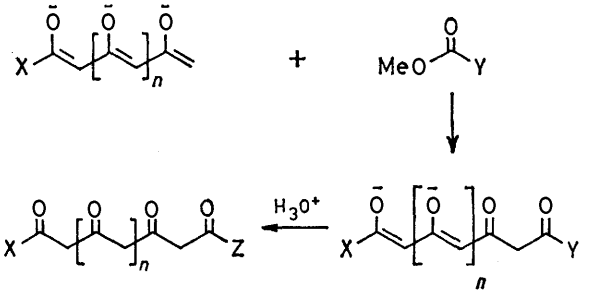
(14)



(15)

Thionyl or phosphoryl chlorides gave polymer but reaction of pentane-2,4-dione with phosgene gave the known [11] 3,5-diacetyl-2,6-dimethyl-4-pyrone (5). Base catalysed condensations of 4-chloropent-3-en-2-one (4) with diethyl or dimethyl malonates gave only pyrones (6a and b); the formation of benzene derivatives was not observed. Clearly, in intermediates (7a or b) facile deprotonation at C-2 prevented terminal enolate formation.

Harris has reported [12] the high yield conversion of methyl 3,5,7-trioxo-octanoate (8a) into methyl orsellinate (1a) although the experimental details have not been published. The condensation of polyanions derived from polyketones or polyketoesters with electrophiles has been widely applied [12] in homologation (Scheme). We considered that the Harris methodology could be modified in order to improve the polyketoester route to alkyl β-resorcylates. Initially, the condensation of the malonate derivative ethyl 3,3-diethoxyprop-2-enoate (9) [13] with the pentane-2,4-dione dianion (10a) was examined. Ester (9) was chosen as a protected malonate to prevent proton transfer to dianion (10a). Dianion (10a), generated with lithium di-isopropylamide or sodium hydride and n-butyl-lithium reacted with ester (9) to give,



X = Me, MeO; Y = Me, MeO, CH=C(Me)-Ō

Z = Me, MeO, CH_2COMe, respectively, *etc.*

SCHEME For convenience, products are shown in non-enolised form

after treatment with pH 9.2 buffer, ethyl orsellinate (1e) (18%) and 2-ethoxycarbonylmethyl-6-methyl-4-pyrone (11) (6%), presumably formed by cyclisation of the intermediate (8b) prior to ester regeneration. The direct condensation of dianion (10a) with dimethyl sodiomalonate was also examined. Prolonged reaction in THF at reflux and treatment of the crude product at pH 9.3 gave methyl orsellinate (1a) (17%). Clearly, the low yield resulted from proton transfer from intermediate (12) to dianion (10a). The reaction was repeated using an excess of dianion (10a); in this way, on cyclisation at higher pH, both methyl orsellinate (1a) (8%) and 2,4,6-trihydroxyacetophenone (30%) were formed. More efficiently, condensation of dimethyl sodiomalonate and dianion (10a) in the presence of excess lithium di-isopropylamide gave methyl orsellinate (1a) (31%). Similarly, dianion (10a) (2 equiv.) with diethyl sodiomalonate gave ethyl orsellinate (1e) (38%).

Harris has reported [12] that the dimerisation of dianion (10b), catalysed by the corresponding monoanion *via* the intermediate trianion (13), gave methyl 3,5,7-trioxo-octanoate (8a) (59%) on work-up. This on silica gave methyl orsellinate (1a) (81%, 48% overall). We have optimised this condensation (Table 1). Reactions at

TABLE 1

Preparation of methyl (1a) and ethyl (1e) orsellinates from methyl and ethyl acetoacetate dianions (10b and c)

No.	Reaction conditions	Yield % of (1a or e)
1	THF (50 ml), 72 h	67
2	Et_2O (50 ml), 6 days	48
3	DME (100 ml), 48 h	69
4	DME (40 ml), 7 days	29
5	DME (10 ml), 8 days	19
6	TMEDA–DME (1 : 9, 50 ml), 48 h	61
7	HMPT–DME (1 : 9, 50 ml), 48 h	56
8	DME (200 ml), reflux, 8 h	76
9	DME (50 ml), reflux, 72 h	50
10	THF (50 ml), 72 h; reflux, 12 h	78
11	DME–THF (3 : 7, 50 ml), reflux, 48 h	54
12	THF (50 ml), 72 h	53
13	DME (50 ml), reflux, 8 h	72

Reactions 1—11 refer to methyl acetoacetate and methyl orsellinate (1a), 12 and 13 to ethyl acetoacetate and ethyl orsellinate (1e). Unless stated, all reactions were carried out at room temperature on the 5 (1, 2, 6, 7, 11—13), 10 (3—5, 9, 10), or 20 g (8) scale. TMEDA refers to *N,N,N′,N′*-tetramethylethylenediamine, DME refers to 1,2-dimethoxyethane, and HMPT to hexamethylphosphoric triamide. In each case the alkyl acetoacetate monoanion was formed with NaH (1 equiv.) and the dianion subsequently with Bu^nLi [(0.9 equiv., entries 1, 6, 7, 11—13) or (0.95 equivalent, all other entries)].

low solvent volume were slow due to reduced dianion (10b or c) solubility (high hexane concentration from n-butyl-lithium). Clearly, reflux in DME or THF were most efficient giving methyl orsellinate (1a) (78% overall).

Syntheses of the β-resorcylate derivatives (1b and c) require a stepwise approach since direct condensation of two different β-ketoesters would give a mixture of products. Ethyl (8c) and methyl (8d) 3,5-dioxohexanoates and methyl 3,5-dioxo-4-methylhexanoate (8e) were prepared *via* the acetoacetic ester dianions and diethyl or dimethyl carbonate. Diketoester (8e) gave pyrone (6c) (78%) with pH 9.2 buffer. The acetylation reactions of the trianions derived from diketoesters (8c—e) with subsequent aromatisation at pH 9.2 giving the β-resorcylate derivatives (1a—c and e) are tabulated (Table 2); DMA (*N,N*-dimethylacetamide) was the reagent of choice. Acetylation reagents capable of stabilising the intermediate (14) by lithium chelation,[14] thus suppressing competitive protonation of the trianion [*e.g.* (10d)], were not successful.

Finally, the β-resorcylate derivatives (1a—c) were prepared in one-pot reactions (see Experimental section). For example, pentane-2,4-dione was treated with sodium hydride, lithium hexamethyldisilazide, dimethyl carbonate, n-butyl-lithium, and DMA in sequence to give methyl orsellinate (1a) (21%) at pH 9. Similarly, 3-methylpentane-2,4-dione and pentane-2,4-dione gave, respectively, analogues (1b and c) (18 and 5%). As an alternative route to (1c) the condensation of the dianion of methyl acetoacetate (10b) and the monoanion of *N,N*-dimethyl-3-oxo-octanamide (15) was examined. Only methyl orsellinate (1a) was detected (t.l.c.). Presum-

ably, the monoanion of (15) was insufficiently electrophilic. The dianion of nonane-2,4-dione and dimethyl sodiomalonate gave methyl 2,4-dihydroxy-6-pentylbenzoate (1c) (10%).

Clearly, optimised syntheses of methyl orsellinate (1a), methyl β-orsinolcarboxylate (1b), and methyl olivetolcarboxylate (1c) are now available. We note with interest recent work [15] on resorcinol synthesis and await to see if it is applicable also to β-resorcylates.

TABLE 2

Acylation reactions of the diketoesters (8c—e)

No.	*Equivalents*, base	Acylating reagent	Reaction * conditions	Product (%)
1	4, $LiNH_2$	EtOAc	48 h	0
2	1, NaH; 2, Bu^nLi	EtOAc	72 h	3
3	3, LDA	EtOAc	4 days	6
4	4, LDA	PhSAc	16 h	36
5	4, LDA	Me_2NAc	16 h	48
6	4, LDA	Ph_2NAc	16 h	Trace
7	4, LDA	Et_2NAc	16 h	11
8	4, LDA	*N*-Acetylimidazole	16 h	30
9	4, LDA	$Me_2NN(Me)Ac$	16 h	13
10	4, $LiN(SiMe_3)_2$	Me_2NAc	16 h	0
11	3, LDA	Me_2NAc	16 h, −20° C	27
12	3, LDA	Me_2NAc	30 min, 0° C	19
13	3, LDA	Me_2NAc	1 h, 0° C	28
14	3, LDA	Me_2NAc	1 h, 15° C	44
15	3, LDA	Me_2NAc	12 h	26
16	3, LDA	Me_2NAc	5 days	11
17	3, LDA	2-(*N*-methylacetamido)pyridine	3 h	16
18	3, LDA	$(Me_2N)_2C{=}NAc$ †	30 min	11
19	3, LDA	$(Me_2N)_2C{=}NAc$ †	3 h	18
20	3, LDA	*N*-acetylpyrrolidine	6 h	10
21	3, LDA	$CH_3(CH_2)_4CONMe_2$	16 h	36
22	3, LDA	Me_2NAc	16 h	18
23	4, LDA	Me_2NAc	16 h	20
24	3, LDA	Me_2NAc	16 h	28
25	3, LDA	Me_2NAc	10 h	36
26	3, LDA	$Me_2NCH_2CH_2N(Me)Ac$	4 h	12
27	3, LDA	*N*-Acetylpyrrolidine	4 h	17

* Reactions 1—9, 10—21, and 22—27 were carried out respectively on diketoesters (8c—e). The products obtained after formation of the trianion, acylation for the times indicated at room temperature (unless otherwise stated), and overnight reaction with pH 9.2 buffer were the β-resorcylates (1e) (entries 1—9), (1a) (entries 10—20), (1c) (entry 21), and (1b) (entries 22—27). LDA refers to lithium di-isopropylamide. † H. Bredereck, G. Simchen, and H. Porkert, *Chem. Ber.*, 1970, **103**, 245.

EXPERIMENTAL

M.p.s were determined on a Kofler hot stage and are uncorrected. Spectra were recorded as liquid films or Nujol mulls (i.r.), in ethanol (u.v.), and in deuteriochloroform (n.m.r.) unless stated to the contrary. All reactions with anions were carried out under dry, oxygen-free nitrogen. Solvents were purified by standard procedures.[16] Petroleum refers to the redistilled fraction with b.p. 60—80 °C. Normal work-up refers to washing with saturated aqueous sodium hydrogencarbonate and brine, drying (Na_2SO_4), and rotary evaporation below 50° C. P.l.c. was carried out on Merck Kieselgel GF_{254}; developing solvents are given in parentheses. Unless stated to the contrary, reactions were carried out at room temperature; detailed procedures are described in the first instance only.

Preparation of 4-*Chloropent*-3-*en*-2-*one* (4).—Phosphorus pentachloride (41.7 g) was added with stirring to pentane-2,4-dione (20.1 g) in diethyl ether (200 ml) at 0 °C. After 0.5 h, the mixture was added to ice–water (300 g). After partial evaporation (to *ca.* 50 ml) the organic phase was stirred with calcium carbonate (9 g) and water (100 ml) at 40 °C for 12 h. The ethereal phase was separated and distilled to give 4-chloropent-3-en-2-one (67%) as the *E*-isomer (4a) (3.45 g), b.p. 42—45 °C at 17 mmHg; n_D^{25} 1.471 7; τ 3.6br (1 H, s), 7.48 (3 H, d, *J* 1 Hz), and 7.8 (3 H, s); the *E*–*Z* isomer mixture (8.31 g), b.p. 46—52 °C at 17 mmHg; n_D^{25} 1.472 8; and the *Z*-isomer (4b) (4.2 g), b.p. 57—61 °C at 17 mmHg; n_D^{25} 1.473 2; $\nu_{max.}$ 1 705s, 1 670s, 1 610s, 1 435m, 1 360s, 1 250m, 1 180s, 1 110m, and 660m cm^{-1}; $\lambda_{max.}$ 233 nm (ε 9 000); τ 3.8br (1 H, s), 7.65 (3 H, s), and 7.78 (3 H, d, *J* 1 Hz); *m/e* 120, 118 (M^+), 103, and 43 (100%). The mixed fraction gave 4-chloropent-3-en-2-one 2,4-dinitrophenylhydrazone, m.p. 186.5—188.5 °C (lit.,[8] 175 °C) (Found: C, 44.35; H, 3.75; N, 18.75; Cl, 11.85. Calc. for $C_{11}H_{11}ClN_4O_4$: C, 44.2; H, 3.7; N, 18.75; Cl, 11.85%). When the calcium carbonate treatment was omitted, 4-chloropent-3-en-2-one (4) (22%) and a by-product, possibly 2,4,4-trichloropent-2-ene (3) (37%), b.p. 70—73 °C at 33 mmHg; n_D^{20} 1.486 9; $\nu_{max.}$ 1 650s, 1 610m, 1 440s, 1 380s, 1 185s, 1 120s, 1 070s, 830s, 810m, 720m, and 665s cm^{-1}; $\lambda_{max.}$ 222 nm (ε 5 400); τ 3.8br (1 H, s), 7.55 (3 H, s), 7.7 (1.5 H, s), and 7.8 (1.5 H, d, *J* 1 Hz); *m/e* 178, 176, 174, 172 (M^+), 139, 137, 103, 101, and 65 (100%) were formed. Pentane-2,4-dione gave 4-chloropent-3-en-2-one (4) with dichlorotriphenylphosphorane (30%) or triphenylphosphine–carbon tetrachloride (68%). Reaction of pentane-2,4-dione with thionyl chloride or phosphoryl chloride gave intractable mixtures.

Reaction of Pentane-2,4-*dione and Phosgene*.—Pentane-2,4-dione (4.1 g), sodium hydride (3.78 g), and imidazole (20 mg) in diethyl ether (60 ml) were refluxed for 3 h, cooled to 0°, and phosgene (57.8 g) in diethyl ether (60 ml) added. After 64 h at room temperature water (150 ml) was added and the organic phase distilled to remove pentane-2,4-dione. The partially sublimed solid was recrystallised from petroleum to give 3,5-diacetyl-2,6-dimethyl-4-pyrone (5) (0.20 g, 5%), m.p. 124—125.5 °C (lit.,[11] 123—124 °C).

Reaction of 4-*Chloropent*-3-*en*-2-*one with Dimethyl Malonate*.—Dimethyl malonate (0.66 g) was added with stirring to potassium t-butoxide (0.60 g) in t-butyl alcohol (20 ml). 4-Chloropent-3-en-2-one (4) (0.50 g) in t-butyl alcohol (10 ml) was added and the mixture stirred overnight. The red-brown suspension was partitioned between ethyl acetate and hydrochloric acid (10% v/v). Normal work-up and p.l.c. (ethyl acetate–dichloromethane 3 : 17) gave 4,6-*dimethyl*-3-*methoxycarbonyl*-2-*pyrone* (6a) (0.19 g, 25%). Recrystallisation from diethyl ether gave needles, m.p. 84—86 °C; $\lambda_{max.}$ 1 740s, 1 700s, 1 650m, 1 560s, 1 440s, 1 350s, 1 260m, 1 195m, 1 040m, 1 020m, 965m, and 815m cm^{-1}, $\lambda_{max.}$ 310 nm (ε 6 200); τ 4.05 (1 H, s), 6.1 (3 H, s), and 7.75 (6 H, s); *m/e* 182 (M^+), 154, 151, 150, 139, 123, 96, 67, 59, and 43 (100%) (Found: C, 59.15; H, 5.75. $C_9H_{10}O$ requires C, 59.35; H, 5.55%). Reaction of dimethyl malonate, 4-chloropent-3-en-2-one (4), and sodium methoxisde in methanol gave the same pyrone (6a) (16%).

Reaction of 4-*Chloropent*-3-*en*-2-*one* (4) *with Diethyl Malonate*.—Diethyl malonate (5.68 g) in ethanol (5 ml) and 4-chloropent-3-en-2-one (4) (4.43 g) in ethanol (5 ml) were added in sequence to sodium ethoxide (2.75 g) in ethanol (30 ml). The mixture was refluxed overnight, cooled, and acetic acid (10 ml) in ethanol (10 ml) added. The mixture was partitioned between diethyl ether and water. After evaporation of the organic phase the mixture was chromato-

graphed on silica (eluant diethyl ether–petroleum 1 : 1) and the resultant yellow oil triturated with petroleum to leave a solid. Crystallisation to constant m.p. gave 4,6-dimethyl-2-pyrone (6b), m.p. 48—49.5 °C (lit.,[17] 50—51 °C).

Reaction of Pentane-2,4-dione with Ethyl 3,3-Diethoxyprop-2-enoate (9).—Pentane-2,4-dione (2.0 g) was slowly added to sodium hydride (0.51 g) and imidazole (5 mg) in THF (25 ml) at 0 °C. After stirring overnight, the mixture was cooled to −78 °C and n-butyl-lithium in hexane (1.53M, 13.2 ml) added. The mixture was allowed to warm slowly to room temperature. After 2 h ethyl 3,3-diethoxyprop-2-enoate[13] (9) (1.9 g) was added. After 2 h stirring, pH 7 buffer (80 ml) was added and the mixture extracted with diethyl ether. The aqueous layer was acidified with hydrochloric acid (10% v/v, 80 ml) and extracted with ethyl acetate. The ethyl acetate was evaporated and the resulting oil (1.24 g) dissolved in pH 9.2 buffer (80 ml). After standing overnight the mixture was acidified and re-extracted with ethyl acetate. After evaporation, the extract was separated by p.l.c. (diethyl ether–petroleum 3 : 7) to give ethyl orsellinate (1e) (368 mg, 18%), m.p. 130—132 °C (lit.,[5] 132 °C), and *2-ethoxycarbonylmethyl-6-methyl-4-pyrone* (11) (112 mg, 6%), m.p. 88—895. °C; $\nu_{max.}$ 1 720s, 1 660s, 1 570s, 1 260s, 1 140m, 1 040m, 900m, and 855m cm^{-1}; $\lambda_{max.}$ 281 nm (ε 5 400); τ 4.05 (1 H, d, *J* 1 Hz), 4.55 (1 H, d, *J* 1 Hz), 5.9 (2 H, q, *J* 7 Hz), 6.4 (2 H, s), 7.75 (3 H, s), and 8.6 (3 H, t, *J* 7 Hz); *m/e* 196 (M^+), 154 (100%), 126, 111, 69, and 43 (Found: C, 61.1; H, 6.1. $C_{10}H_{12}O$ requires C, 61.2; H, 6.15%).

Reaction of Pentane-2,4-dione with Dimethyl Malonate.—(a) n-Butyl-lithium in hexane (1.4M, 21.5 ml) was added to di-isopropylamine (4.2 ml) in THF (20 ml) at −78 °C. After 2 h pentane-2,4-dione (1.0 ml) was added. After stirring overnight at room temperature, the clear yellow solution was added to dimethyl sodiomalonate [from sodium hydride (360 mg) and dimethyl malonate (1.16 g)] in THF (30 ml). After reflux for 48 h the mixture was quenched with hydrochloric acid (10% v/v). The pH was adjusted to 9.3 with saturated aqueous potassium carbonate. After 2 h stirring, the mixture was acidified and extracted with ethyl acetate. Evaporation and p.l.c. of the organic phase gave methyl orsellinate (1a) (244 mg, 17%), m.p. 135—139 °C (lit.,[18] 135—139 °C).

(b) A solution of the dianion of pentane-2,4-dione [from dione (2.1 g), sodium hydride (0.51 g), and n-butyl-lithium in hexane (1.58M, 13.5 ml)] in THF (20 ml) was added to dimethyl sodiomalonate [from dimethyl malonate (1.4 g) and sodium hydride (0.26 g)] in THF (30 ml). After reflux for 48 h the mixture was added to water (50 ml) and extracted with diethyl ether. After stirring overnight, the aqueous phase was extracted with ethyl acetate. Evaporation of the organic phase and p.l.c. gave methyl orsellinate (1a) (156 mg, 8%) and 2,4,6-trihydroxyacetophenone (516 ing, 30%), m.p. 214—218 °C (lit.,[19] 218—219 °C).

(c) Pentane-2,4-dione (1.05 ml) was added to a suspension of sodium hydride (315 mg) and imidazole (10 mg) in THF (30 ml). After stirring overnight at room temperature, the mixture was cooled to −78 °C. Di-isopropylamine (1.4 ml) and n-butyl-lithium in hexane (1.4M, 14.5 ml) were added and the mixture warmed to room temperature overnight. After addition to a suspension of dimethyl sodiomalonate (155 mg) and having been heated to reflux for 48 h the reaction mixture was worked up as above (1) to give methyl orsellinate (1a) (56p mg, 31%).

Reactions of Pentane-2,4-dione with Diethyl Malonate.—(a) Pentane-2,4-dione (2.0 g), sodium hydride (0.5 g), and imidazole (10 mg) in THF (30 ml) were stirred at room temperature overnight before cooling to −78 °C and adding n-butyl-lithium in hexane (1.53M, 13.1 ml). Having warmed to room temperature, the resulting solution was slowly added to a suspension of diethyl sodiomalonate (1.95 g) in THF (20 ml). The mixture was heated to reflux for 48 h before being quenched with 10% (v/v) hydrochloric acid and extracted with ethyl acetate. After evaporation of ethyl acetate, the oily product (2.2 g) was stirred with pH 9.2 buffer solution (30 ml) for 12 h. Acidification and re-extraction with ethyl acetate gave a crude product (2.0 g) which was triturated with petroleum. The residue was dissolved in diethyl ether, boiled with decolourising charcoal, and filtered through a pad of silica. The ether was evaporated to leave a semi-crystalline residue (1.0 g) which was recrystallised from benzene–petroleum to give ethyl orsellinate (1e) (0.71 g, 34%).

(b) A similar reaction was carried out in refluxing 1,2-dimethoxyethane (50 ml) for 24 h to give ethyl orsellinate (1e) (0.8 g, 38%).

Self-condensation of Methyl Acetoacetate (*Typical Procedure*).—Methyl acetoacetate (5.0 g) was slowly added to a stirred suspension of sodium hydride (1.02 g) and imidazole (10 mg) in THF (50 ml). After stirring overnight, the mixture was cooled to −78 °C and n-butyl-lithium in hexane (1.53M, 26.0 ml) was added. After warming to room temperature and stirring for three days, the mixture was quenched with 10% (v/v) hydrochloric acid and extracted with ethyl acetate. Evaporation of ethyl acetate gave an oil which was treated with pH 9.2 buffer solution (30 ml) for 12 h before acidification and re-extraction with ethyl acetate. Evaporation of the ethyl acetate gave a crystalline material (2.3 g) which was recrystallised from benzene–petroleum to give methyl orsellinate (1a) (1.7 g, 50%).

Preparation of Ethyl 3,5-Dioxohexanoate (8c).—Pentane-2,4-dione (10.0 g) was slowly added to a suspension of sodium hydride (2.7 g) and imidazole (50 mg) in THF (100 ml). After stirring overnight the mixture was cooled to −78 °C and n-butyl-lithium in hexane (1.6M, 63 ml) added and the mixture allowed to slowly warm up to 0 °C. Diethyl carbonate (11.9 g) was added and stirring continued at room temperature overnight. The mixture was added to 10% hydrochloric acid (100 ml) and extracted with ethyl acetate. The crude product (9.5 g) after evaporation of the organic phase was distilled under reduced pressure to give ethyl 3,5-dioxohexanoate (8c) (4.5 g, 26%), b.p. 69—72 °C at 0.07 mmHg (lit.,[20] 110 °C at 3 mmHg); $\lambda_{max.}$ 275 nm (ε 6 500), $\lambda_{max.}$ (EtOH–NaOH) 295 nm (ε 15 000).

Methyl 3,5-Dioxohexanoate (8d).—Pentane-2,4-dione (1.0 g) was stirred with a suspension of sodium hydride (0.33 g) and imidazole (20 mg) in THF (25 ml) for 12 h. After cooling to −78 °C, 1,1,1,3,3,3-hexamethyldisilazane (1.65 g) and n-butyl-lithium in hexane (1.4M, 14.4 ml) were added. The mixture was stirred at room temperature for 6 h and recooled to −78 °C when dimethyl carbonate (0.95 g) was added. After warming to room temperature overnight, the mixture was partitioned between ethyl acetate and 10% hydrochloric acid. The crude product from the organic phase was purified by p.l.c. (diethyl ether–petroleum 3 : 7) to give methyl 3,5-dioxohexanoate (8d) (1.07 g, 68%), b.p. 58—68 °C at 0.2 mmHg (lit.,[21] 65 °C at 11 mmHg); n_D^{24} 1.469 7; $\lambda_{max.}$ (MeOH) 272 nm (ε 7 700), $\lambda_{max.}$ (MeOH–NaOH) 294 nm (ε 18 000).

Preparation of Methyl 3,5-*Dioxo*-4-*methylhexanoate* (8e).—3-Methylpentane-2,4-dione (1.0 g) was added to a solution of lithium 1,1,1,3,3,3-hexamethyldisilazide [from n-butyllithium in hexane (1.4M, 19.0 ml) and 1,1,1,3,3,3-hexamethyldisilazane (4.3 g)] in THF (20 ml) at −78 °C. The mixture was stirred for 4 h at room temperature and recooled to −78 °C, when dimethyl carbonate (0.8 g) was added. The mixture was allowed to warm to room temperature overnight before being partitioned between ethyl acetate and 10% (v/v) hydrochloric acid. After evaporation of the ethyl acetate, the crude product (2.0 g) was purified by p.l.c. to give *methyl* 3,5-*dioxo*-4-*methylhexanoate* (8e) (842 mg, 71%), b.p. 84—90 °C at 0.65 mmHg; n_D^{18} 1.438 8; $\nu_{max.}$ 2 960s, 2 880m, 1 740s, 1 630m, 1 570m, 1 440m, 1 260s, and 1 150m cm^{-1}; 286 (ε 1 000) and 273 nm (ε 2 600); τ (CCl) 6.3 $\lambda_{max.}$ (3 H, s), 6.6 (1 H, s), 6.65 (1 H, s), 7.85 (3 H, d, *J* 2 Hz), 8.2 (1.5 H, s), and 8.7 (1.5 H, d, *J* 2 Hz) (*ca.* 50% enol); *m/e* 172 (M^+) 140, 130, 101, 99, 98, and 43 (100%) (Found: C, 55.55; H, 7.2. $C_8H_{12}O$ requires C, 55.8; H, 7.0%).

Preparation of 2-(N-*Methylacetamido*)*pyridine*.—2-Acetamidopyridine [22] (3.27 g) and potassium t-butoxide (3.23 g) were heated to reflux for 30 min in THF (50 ml). After cooling to room temperature, methyl iodide (3.0 ml) was added and the mixture heated to reflux for 12 h. Filtration and evaporation of the solvent gave an oil which was distilled under reduced pressure to give 2-(N-*methylacetamido*)-*pyridine* (2.71 g, 75%), b.p. 75—77 °C at 0.3 mmHg; n_D^{22} 1.537 4; $\nu_{max.}$ 1 670s, 1 590s, 1 575m, 1 475s, 1 430s, 1 380s, 1 345m, 1 300m, 1 140m, 995m, 980m, 790m, and 750m cm^{-1}; $\lambda_{max.}$ 230 (ε 6 000) and 265 nm (3 600); τ (CCl) 1.55br (1 H, d, *J* 4 Hz), 2.1—3.0 (3 H, m), 6.6 (3 H, s), and 7.95 (3 H, s), *m/e* 150 (M^+), 108 (100%), 107, 80, 79, and 57 (Found: C, 63.8; H, 6.9; N, 18.45. $C_8H_{10}N_2O$ requires C, 63.95; H, 6.7; N, 18.65%).

Preparation of 5,6-*Dimethyl*-4-*hydroxy*-2-*pyrone* (6c).—Methyl 4-methyl-3,5-dioxohexanoate (8e) (100 mg) was stirred with pH 9.2 buffer (10 ml) for 16 h. Acidification, extraction with ethyl acetate and recrystallisation from chloroform gave 4-hydroxy-5,6-dimethyl-2-pyrone (6c) (64 mg, 78%), m.p. 194—198 °C (lit.,[23] 204—206 °C); $\nu_{max.}$ 3 300br,s, 1 665s, 1 615m, 1 565s, and 1 265s, cm^{-1}; $\lambda_{max.}$ 380 nm (ε 5 600); τ ([$^2H_6$]-acetone–$CDCl_3$) 4.55 (1 H, s), 7.8 (3 H, s), and 8.1 (3 H, s); *m/e* 140 (M^+), 112, 83, 70, 56, and 43

Acetylation of Ethyl 3,5-*Dioxohexanoate* (8c).—Ethyl 3,5-dioxohexanoate (8c) (0.50 g) was added to lithium di-isopropylamide [from n-butyl-lithium in hexane (1.72M, 6.8 ml) and di-isopropylamine (1.75 ml)] in THF (30 ml) at −78 °C. After slowly warming to and stirring at room temperature for 4 h, the mixture was cooled to 0 °C and *N*,*N*-dimethylacetamide (0.5 ml) in THF (5 ml) slowly added. Stirring was continued at room temperature overnight when the mixture was quenched with 10% (v/v) hydrochloric acid and extracted with ethyl acetate. Evaporation of the ethyl acetate gave a crude product which was stirred with pH 9.2 buffer solution (10 ml) for 12 h. Acidification and re-extraction, followed by p.l.c. (diethyl ether–petroleum 3 : 7) gave ethyl orsellinate (1e) (275 mg, 48%).

Acetylation of Methyl 3,5-*Dioxo*-4-*methylhexanoate* (8e).—*N*,*N*-Dimethylacetamide (3.5 ml) was added to the trianion of methyl 4-methyl-3,5-dioxohexanoate (8e) [from n-butyllithium in hexane (1.54M, 37 ml), di-isopropylamine (8.0 ml) and (8e) (2.93 g)] in THF (30 ml) at −78 °C. After warming to room temperature and stirring for 12 h, the mixture was poured into 10% hydrochloric acid (50 ml) and the pH of the solution adjusted to 9 with saturated potassium carbonate solution. After immediate extraction with petroleum, the aqueous phase was stirred overnight before being acidified and extracted with ethyl acetate. Evaporation of the ethyl acetate gave a semi-crystalline crude product (1.56 g) which was sublimed at 120 °C and 10^{-4} mmHg to give methyl 2,4-dihydroxy-3,6-dimethylbenzoate (1b) contaminated by (*ca.* 5%) n-butyl 2,4-dihydroxy-3,6-dimethylbenzoate (1f) (780 mg) (presumably formed from Bu^nOLi impurities). A portion was purified by p.l.c. (diethyl ether–petroleum 3 : 7) to give pure methyl 2,4-dihydroxy-3,6-dimethylbenzoate (1b), m.p. 143—145 °C (from diethyl ether–petroleum) (lit.,[24] 143—144 °C) (Found: C, 61.4; H, 6.25. Calc. for $C_{10}H_{12}O_4$: C, 61.2; H, 6.15%) and pure n-butyl 2,4-dihydroxy-3,6-dimethylbenzoate (1f) sublimed at 100 °C and 0.2 mmHg, m.p. 122—123 °C (lit.,[25] 123 °C); *m/e* 238 (M^+), 196, 164 (100%), 149, 136, 57, and 43 (Found: C, 65.6; H, 7.5. Calc. for $C_{13}H_{18}O_4$: C, 65.55; H, 7.6%).

Reaction of Methyl 3,5-*Dioxohexanoate* (8d) *with* N,N-*Dimethyl*-*n*-*hexanamide*.—*N*,*N*-Dimethyl-n-hexanamide (607 mg) was added to the trianion of methyl 3,5-dioxohexanoate [from n-butyl-lithium in hexane (1.54M, 4.0 ml), di-isopropylamine (0.90 ml), and methyl 3,5-dioxohexanoate (8d) (296.0 mg)] in THF (10 ml) at −20 °C. After stirring for 5 h, the mixture was poured into 10% (v/v) hydrochloric acid and the pH of the solution adjusted to 9.5 with saturated aqueous potassium carbonate and left to stand overnight. The solution was acidified and extracted with ethyl acetate to give a crude oily product. P.l.c. (diethyl ether–petroleum 3 : 7) gave methyl 2,4-dihydroxy-6-pentylbenzoate (1c) (164.0 mg, 36%), m.p. 72—75 °C (lit.,[26] 76—77 °C); *m/e* 238 (M^+) 206, 182, 150, 124, 82, 73, 43, and 41.

Preparation of Methyl Orsellinate (1a) *from Pentane*-2,4-*dione*.—n-Butyl-lithium in hexane (1.51M, 2.64 ml) and 1,1,1,3,3,3-hexamethyldisilazane (344 mg) were added at −78 °C to a suspension of the sodium salt of pentane-2,4-dione (200 mg, 2.0 mmol) [made with sodium hydride (76 mg)] in THF (6 ml) and the mixture was stirred overnight at room temperature. After cooling to −78 °C, dimethyl carbonate (182 mg) was added and the mixture was slowly warmed to room temperature for 4 h before being recooled to −78 °C. n-Butyl-lithium in hexane (1.51M, 3.31 ml) was added and the mixture warmed to room temperature and stirred overnight. After recooling to −20 °C, *N*,*N*-dimethylacetamide (0.5 ml)was added and stirring continued for 6 h. The mixture was poured into 10% (v/v) hydrochloric acid (15 ml) and the pH of the solution adjusted to 9 with saturated aqueous potassium carbonate. After 3 h the solution was acidified to pH 2 and extracted with ethyl acetate. Evaporation of the ethyl acetate gave a crude product which was purified by p.l.c. to give methyl orsellinate (1a) (76.8 mg, 21%).

Methyl 2,4-*Dihydroxy*-3,6-*dimethylbenzoate* (1b) *from* 3-*Methylpentane*-2,4-*dione*.—The previous method was followed for the synthesis of methyl 2,4-dihydroxy-3,6-dimethylbenzoate (1b) (31.8 mg, 18%). Sodium hydride (118.4 mg), 1,1,1,3,3,3-hexamethyldisilazane (0.35 ml), n-butyl-lithium in hexane (0.77M, 4.6 ml), and dimethyl carbonate (156 mg) were used to form the dianion of methyl 4-methyl-3,5-dioxohexanoate (8e) *in situ*. Addition of di-isopropylamine (0.75 ml) and n-butyl-lithium in hexane (0.77M, 6.9 ml) at −78 °C, to form the trianion, was followed by the addition of *N*,*N*-dimethylacetamide (0.60 ml) at

room temperature. The mixture was stirred for 30 min before being worked-up as above.

Methyl 2,4-Dihydroxy-6-pentylbenzoate (1c) *from Pentane-2,4-dione*.—The dianion of methyl 3,5-dioxohexanoate (8d) was formed *in situ* from pentane-2,4-dione (200 mg) and dimethyl carbonate (185 mg), using sodium hydride (90.4 mg), 1,1,1,3,3,3-hexamethyldisilazane (0.37 mg), and n-butyl-lithium in hexane (1.49M, 2.7 ml) in THF (20 ml). The resulting solution was cooled to −78 °C and di-isopropylamine (618 mg) and n-butyl-lithium in hexane (1.49M, 4.0 ml) added. After warming to room temperature and stirring overnight, the mixture was cooled to −20 °C and *N,N*-dimethyl-n-hexanamide (923 mg) was added. Stirring was continued for 4 h before quenching and working-up as above. P.l.c. of the crude product gave methyl 2,4-dihydroxy-6-pentylbenzoate (1c) (24.8 mg, 5%).

N,N-*Dimethyl-3-oxo-octanamide* (15).—1-Bromobutane (20 ml) was added to the dianion of *N,N*-dimethyl-3-oxobutanamide [27] (2.0 g) [from sodium hydride (773 mg) and n-butyl-lithium in diethyl ether (1.5M, 10.5 ml)] in THF (50 ml) at 0 °C. After warming to room temperature and stirring for 1.5 h the mixture was acidified with 10% hydrochloric acid and extracted with ethyl acetate. The crude product (2.7 g) from evaporation of the organic phase was distilled to give *N,N-dimethyl-3-oxo-octanamide* (15) (2.16 g, 75%), b.p. 136—140 °C, at 1.8 mmHg; n_D^{23} 1.467 4; $\nu_{max.}$ 3 500br,s, 2 940m, 1 670br,s, 1 590s, 1 575m, 1 480s, 1 440s, 1 380s, 1 350m, 1 300m, 1 140s, 995m, 980m, 790s, and 750s cm^{-1}; $\lambda_{max.}$ 254 nm (ε 3 500), $\lambda_{max.}$ (NaOH–EtOH) 279 nm (ε 5 600); τ 5.0 (0.33 H, s), 6.6 (1.33 H, s), 7.05br (6 H, s), and 7.4—9.3 (11 H, m) (33% enol); *m/e* 185 (M^+) 142, 129, 114, 87, 72, and 45 (100%)(Found: C, 64.8; H, 10.6; N, 7.25. $C_{10}H_{19}NO_2$ requires C, 64.85; H, 10.35; N, 7.55%).

On heating to reflux, the monoanion of *N,N*-dimethyl-3-oxo-octanamide (15) (1.6 g) [from sodium hydride (0.5 g)] with the dianion of methyl 3-oxobutanoate (1.0 g) [from sodium hydride (400 mg) and n-butyl-lithium in hexane (1.42M, 6.3 ml)] for 48 h, the only product to be observed was methyl orsellinate (1a) (t.l.c.).

Reaction of Nonane-2,4-dione with Dimethyl Malonate.—The dianion of nonane-2,4-dione (1.0 g) [from sodium hydride (232 mg), di-isopropylamine (0.90 ml), and n-butyl-lithium in hexane (1.3M, 10.0 ml)] in THF (20 ml) was added to the monoanion of dimethyl malonate (0.75 ml) [from sodium hydride (234 mg)] in THF (30 ml). The mixture was heated to reflux for 48 h before pouring into 10% hydrochloric acid. The pH was adjusted to 9 and the solution left to stand at room temperature overnight. Reacidification and extraction with ethyl acetate gave a crude product (1.2 g) which was purified by t.l.c. to give methyl 2,4-dihydroxy-6-pentylbenzoate (1c) (153 mg, 10%).

We thank the S.R.C. for support.

[9/1567 *Received*, 2nd *October*, 1979]

REFERENCES

[1] R. Valters and O. Neilands, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 1968, 710; R. M. Anker and A. H. Cook, *J. Chem. Soc.*, 1945, 311; R. S. Marmor, *J. Org. Chem.*, 1972, **37**, 2901; C. R. Smith, *ibid.*, 1960, **25**, 588; A. M. Cohen, Ger. Offen., 2,359,233 (*Chem. Abs.*, 1974, **81**, 91,219q); K. K. Light and H. Ulstein, Ger. Offen., 2,163,323 (*Chem. Abs.*, 1972, **77**, 151,681p); A. Sonn, *Ber.*, 1928, **61**, 926; R. A. Kloss and D. A. Clayton, *J. Org. Chem.*, 1965, **30**, 3566; L. Cleaver, J. A. Crofts, E. Richie, and W. C. Taylor, *Austral. J. Chem.*, 1976, **29**, 1989; A. St. Pfau, *Helv. Chim. Acta*, 1933, **16**, 282; R. D. Grossman, R. S. DeSimone, and L. G. Heeringa, Ger. Offen., 1,941,041 (*Chem. Abs.*, 1971, **74**, 79,502z); J. D. Grossman, R. S. DeSimone, and L. G. Heeringa, U.S.P. 3,634,491 (*Chem. Abs.*, 1972, **77**, 88,098m); J. D. Grossman, R. S. DeSimone, and L. G. Heeringa, Ger. Offen., 1,966,337 (*Chem. Abs.*, 1972, **77**, 101,207t); K. K. Light and R. W. Wilson, *Internat. Congress Essent. Oils*, 1974, **6**, 135; K. Kulka and T. Zazula, U.S.P., 3,884,843 (*Chem. Abs.*, 1975, **83**, 78,903e); A. Brossi, A. Focella, and S. Teitel, U.S.P., 3,919,322 (*Chem. Abs.*, 1976, **84**, 43,460b); H. Kurihara and K. Kobayashi, Japan Kokai 76 13,736 (*Chem. Abs.*, 1976, **85**, 53,90s); T. Nishimura, T. Kawanobe, K. Kogani, and K. Hayashi, Japan Kokai 76 110,530 (*Chem. Abs.*, 1977, **86**, 89,420h).

[2] G. M. Gaucher and M. G. Shepherd, *Biochem. Prep.*, 1971, **13**, 70.

[3] M. V. Sargent, P. Vogel, and J. A. Elix, *J.C.S. Perkin I*, 1975, 1986.

[4] H. Tsuruta, T. Hagiwara, and T. Yoshida, Japan Kokai, 76 100,038 (*Chem. Abs.*, 1977, **86**, 72,221w).

[5] R. N. Mirrington, E. Ritchie, C. W. Shoppee, S. Sternhell, and W. C. Taylor, *Austral. J. Chem.*, 1966, **19**, 1265.

[6] J. Santesson, *Acta Chem. Scand.*, 1970, **24**, 3373.

[7] K. K. Light, U.S.P. 3,928,419 (*Chem. Abs.*, 1976, **84**, 105,224p).

[8] M. Julia, *Ann. Chim.* (*France*), 1950, **5**, 595.

[9] L. Gruber, I. Tomoskozi, and L. Radics, *Synthesis*, 1975, 708.

[10] R. D. Clark and C. H. Heathcock, *J. Org. Chem.*, 1976, **41**, 636.

[11] L. I. Belen'kii, G. P. Gromova, and Ya. L. Gol'dfarb, *Khim. Geterotsikl. Soedinenii*, 1972, 591.

[12] T. M. Harris and C. M. Harris, *Tetrahedron*, 1977, **33**, 2159 and references therein.

[13] S. A. Glickman and A. C. Cope, *J. Amer. Chem. Soc.*, 1945, **67**, 1017.

[14] D. Comins and A. I. Meyers, *Synthesis*, 1978, 403.

[15] A. A. Jasca-Chamiec, P. G. Sammes, and P. D. Kennewell, *J.C.S. Chem. Comm.*, 1978, 118.

[16] D. D. Perrin, W. L. F. Armarego, and D. R. Perrin, ' Purification of Laboratory Chemicals,' Pergamon Press, Oxford, 1966.

[17] R. H. Wiley and N. R. Smith, *J. Amer. Chem. Soc.*, 1952, **74**, 3893.

[18] G. Buchi, J. D. White, and G. N. Wogan, *J. Amer. Chem. Soc.*, 1965, **87**, 3484.

[19] D. J. Ringshaw and H. J. Smith, *Chem. and Ind.*, 1965, 1383.

[20] S. Gelin and R. Gelin, *Bull. Soc. chim. France*, 1969, 231.

[21] C. T. Bedford, J. M. Forrester, and T. Money, *Canad. J. Chem.*, 1970, **48**, 2645.

[22] L. W. Deady and J. A. Zoltewicz, *J. Org. Chem.*, 1972, **37**, 603.

[23] T. M. Harris, C. M. Harris, and M. P. Wachter, *Tetrahedron*, 1968, **24**, 6897.

[24] T. K. Murty, *J. Sci. Ind. Research*, 1960, **19B**, 508.

[25] H. Huzikawa, *J. Pharm. Soc. Japan*, 1940, **60**, 473.

[26] P. Djura and M. V. Sargent, *Austral. J. Chem.*, 1976, **29**, 1069.

[27] H. Bredereck, R. Gompper, and K. Llemm, *Chem. Ber.*, 1959, **92**, 1456.