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BIOGENETIC-TYPE SYNTHESIS OF POLYKETIDES PART VIII*

EXPERIMENTS WITH THE TETRA- AND HEXA-ACETATE SYSTEMS

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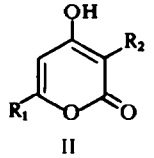
Abstract—Syntheses of a number of 4-oxygenated 2-pyrones, including the ethionine-induced metabolite of *Penicillium stipitatum*, tetraacetic lactone (III) are described. The use of these compounds in devising biogenetic-type syntheses of naturally-occurring polyketides is explored.

ALTHOUGH many of the details of the pathway of fatty acid biosynthesis have been established in cell free systems,[1] our knowledge of the processes involving the decarboxylative polymerization of acetyl and malonyl units to yield phenolic compounds via their enzyme-bound thiol esters, in conformity with the oxygenation patterns predicted by Birch's theory,[2] has so far been confined at the cell-free level to the fermentations producing 6-methylsalicylic acid (6-MSA),[3,4,5,6] patulin,[7] orsellinic acid[8] and its 5-methyl derivative,[9] stipitatic acid,[10,11] and alternariol.[12] From these studies it is clear that the "polyacetate" hypothesis[2] has been vindicated, but so far all of the evidence for the intervention of a poly-β-carbonyl chain (as I) has been indirect.

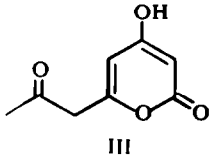
$$CH_3(COCH_2)_nCO—S\text{-enzyme}$$

(I)

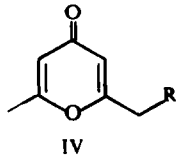
Subsequent to our earlier attempts to provide models for the synthesis and reactions of (I; $n > 3$) using the reactivity and hydrolytic behaviour of the 4-hydroxy-2-pyrone template (II), evidence has accumulated that monopyrones closely related to these models such as triacetic lactone, TAL (II; $R_1 = CH_3$; $R_2 = H$), 3-methyl-TAL (II; $R_1 = R_2 = CH_3$), tetraacetic lactone (III), 2,6-dimethyl pyrone[9] (IV; R = H) and, by implication, the acid (IV: $R = CO_2H$) are formed by fungal systems normally producing phenolic metabolites.



II



III



IV

Moreover, these structures represent aberrant yet structurally informative polyketides which are not intermediates for the aromatic compounds of the host organism.

* Part VII. H. Guilford, A. I. Scott, D. Skingle and M. Yalpani, *Chem. Comm.* 1127 (1968).

Whilst these metabolites and our synthetic models (as II) do not fulfil the role of obligatory precursors of the C_8 aromatic series (e.g. orsellinic acid, 6-MSA) it was felt that a more detailed study of their chemistry might not only provide *in vitro* models for cyclization sequences in aromatic biosynthesis but, more importantly, could be modified to coincide at strategic points with some of those postulated intermediates (albeit enzyme-bound) which are believed to lie on the pathway between acetyl coenzyme A and the phenols of Nature.[3]

The first phases of the enzymic process which have received comment concern the formation of aceto–acetate via the decarboxylative condensation of acetate and malonate units esterified to the sulphydryl groups of a multi-enzyme complex. The subsequent steps consist of decarboxylative addition of two malonyl units and reduction to reach the C_8 enzyme bound intermediate (Scheme 1) according to the postulate of Lynen and Tada.[3]

SCHEME I

$$CH_3COCH_2COSEnz + CH_2(CO_2H)COSEnz \rightleftharpoons CH_3COCH_2COCH_2COSEnz$$

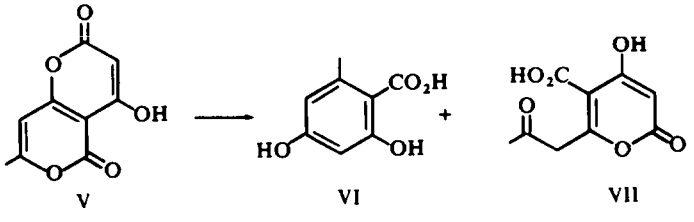
$$CH_3COCH_2COCH_2COSEnz \xrightleftharpoons{NADPH} CH_3COCH_2CH(OH)CH_2COSEnz$$

$$CH_3COCH_2CH(OH)CH_2COSEnz \xrightleftharpoons{-H_2O} CH_3COCH_2CH{=}CHCOSEnz$$

$$CH_3COCH_2CH{=}CHCOSEnz \rightleftharpoons CH_3COCH_2CH{=}CHCOCH_2COSEnz$$

$$+ CH_2(CO_2H)COSEnz$$

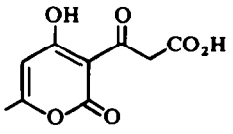
As a prelude to studies on the cell free biosynthesis of phenolic metabolites, our immediate objective was the preparation of the putative C_8 intermediate of Scheme 1 utilizing the chemistry of 4-hydroxy 2-pyrone and its homologues, in particular their selective hydrolysis and reduction. Thus as a result of our earlier studies the dipyrone (V) became readily available and was first studied as a source of tetraacetic lactone (III).



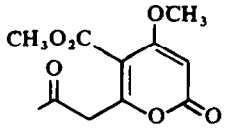
V VI VII

It had been shown that orsellinic acid (VI) was formed in 6% yield when V was hydrolysed with KOH aq.[13] Reinvestigation of this hydrolysis-cyclisation reveals that brief (10 min) treatment of V in 2M KOH aq affords a mixture of orsellinic

acid (19%) and a new acid (44%) $C_9H_8C_6$ m.p. 280° to which we have assigned structure VII *viz.* tetraacetic lactone-5-carboxylic acid. Thus VII could be distinguished from the other possible hydrolysis product (VIII) by methylation with CH_2N_2 to give 4-methoxy-5-carbomethoxy-6-acetonyl-2-pyrone (IX), identical with a sample prepared by another method.[14]

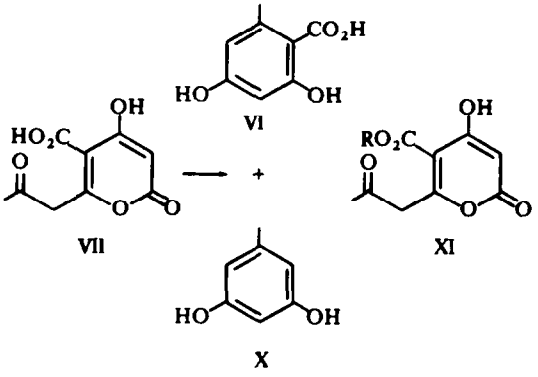


VIII



IX

Further treatment of VII with aqueous or methanolic KOH gave orsellinic acid (VI) and orcinol (X). With $Mg(OMe)_2$[15] a *salt* was obtained from which the starting acid was recovered on acidification. The corresponding esters (XI, R = CH_3, C_2H_5) could be preferentially hydrolysed and relactonized back to the dipyrone (V). The same result (dipyrone formation) was achieved in attempts to form ketals of the side chain ketonic function.



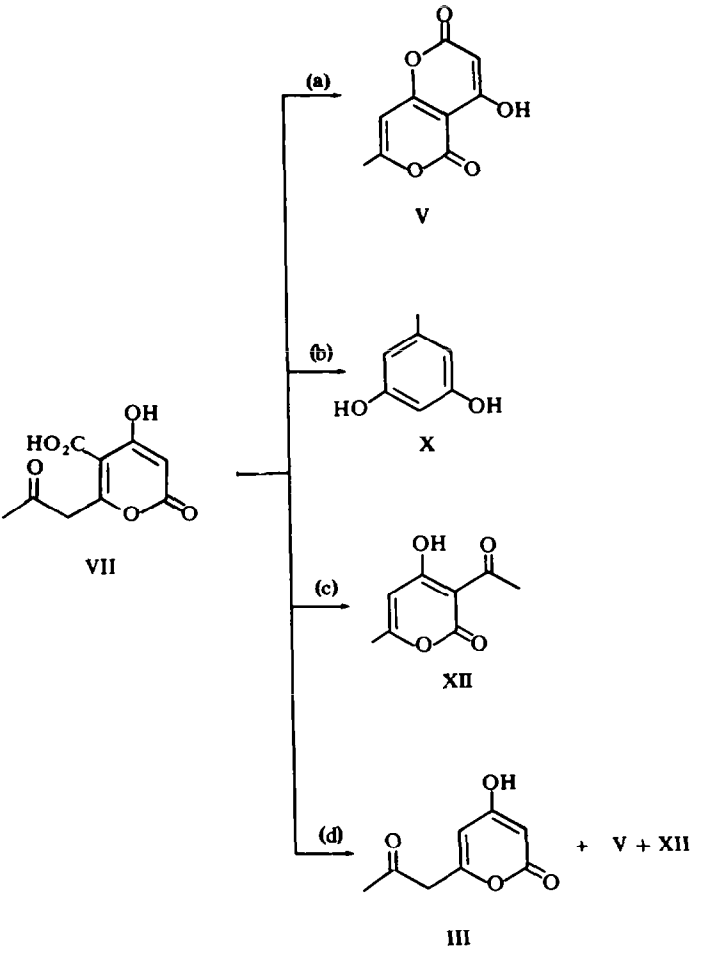
VI

VII

XI

X

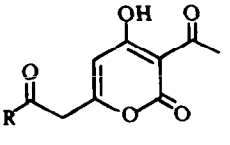
However, the most important feature of the acid (VII) is that its decarboxylation should provide a total synthesis of tetraacetic lactone (III) a compound first reported by Bentley and Zwitkowits[16] as an ethionine-induced metabolite of the tropolone-producing organism *P. stipitatum*. In practice controlled removal of CO_2 from VII proved to be unexpectedly difficult, orsellinic acid (VI) and orcinol (X) being produced under a variety of conditions (Experimental Section). At pH 5·5 treatment of VII with Cu bronze leads to dehydroacetic acid (XII) presumably by relactonization, hydrolysis of the second ring, and decarboxylation of the resultant keto acid (VIII). The desired reaction conditions were finally found when VII was refluxed in dry dioxan containing Cu bronze. From this experiment tetraacetic lactone (III) could be isolated in 38% yield, m.p. 119–120° and was identical in every respect with authentic material (m.p. 119–120°) provided by Dr. R. Bentley (m.p., m. m.p., UV, NMR and mass spectra). The other identifiable products of this reaction were unreacted acid (10%), dehydroacetic acid (XII; 4%) and dipyrone (V; 23%).



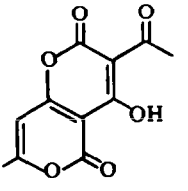
V X VII XII III

Conditions (a) Sublime
(b) Heat/quinoline/Cu bronze
(c) Reflux pH/Cu bronze
(d) Reflux/dioxane/Cu bronze

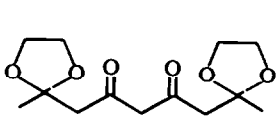
In addition to confirming Bentley's observations on the formation of orsellinic acid we have now examined some further reactions of III and compared them with those of structurally related compounds.



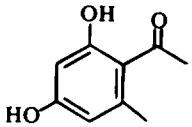
XIII



XIV

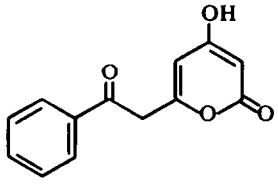


XV

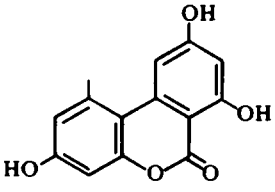


XVI

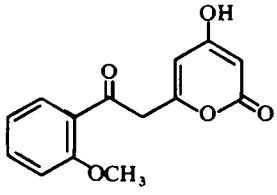
Refluxing tetraacetic lactone (III) with AcOCl in CF_3COOH leads to a 40% yield of 3-acetyl-tetraacetic acid lactone (XIII; R = CH_3). The latter compound can be recovered from 0·5M methanolic NaOH after 17 hr at room temperature, but decomposes to unknown fragments on treatment with stronger base. This is also the case with 3-acetyl-6-phenacyl-4-hydroxy-2-pyrone (XIII; R = C_6H_5), prepared by the method of Harris and Harris.[17] In view of the reported rearrangement of 3'-acetyl-dipyrone (XIV)[13] and of the protected tetraketone (XV)[18] to orcacetophenone (XVI) this result was perhaps somewhat surprising.



XVII

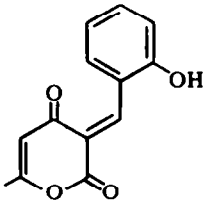


XVIII

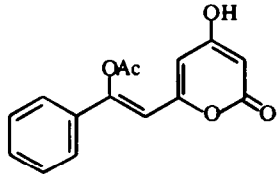


XIX

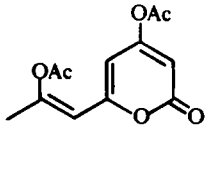
6-Phenacyl-4-hydroxy-2-pyrone (XVII) was prepared in 17% yield by deacylation of (XIII; R = C_6H_5) with 90% H_2SO_4 or in 44% yield by the reaction of triacetic lactone (II; R_1 = CH_3; R_2 = H) with methyl benzoate in liquid NH_3. As a closer model for the biosynthesis of the naturally occurring acetate-derived biphenyl alternariol (XVIII) 6-(2-methoxy-phenacyl)-4-hydroxy-2-pyrone (XIX) was similarly prepared in 9% yield from II, (R_1 = CH_3; R_2 = H) and methyl 2-methoxy-benzoate. On the other hand treatment of salicylaldehyde with triacetic lactone under these conditions afforded the adduct XX in 22% yield.



XX

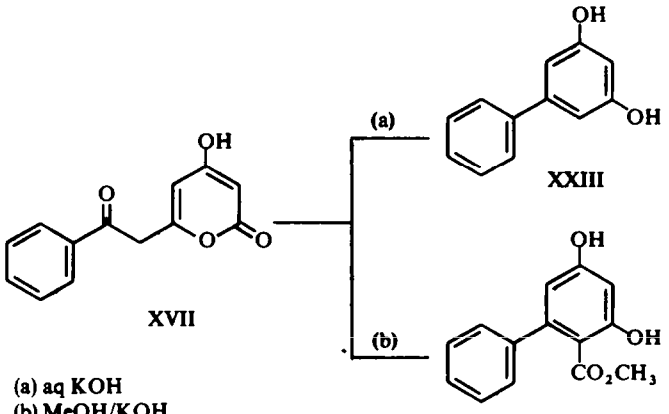


XXI

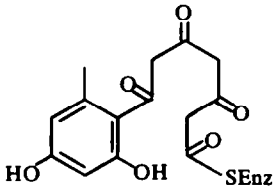


XXII

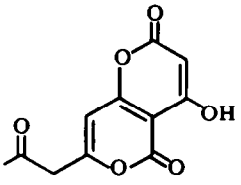
III, XIII, (R = C_6H_5) and XVII on treatment with one equivalent of acetic anhydride in pyridine yield enol acetates XXI, (R_1 = CH_3; R_2 = H), XXI, (R_1 = C_6H_5; R_2 = CH_3CO) and XXI, (R_1 = C_6H_5; R_2 = H) respectively. Treatment of III with excess of this reagent affords the diacetate (XXII).



6-Phenacyl-4-hydroxy-2-pyrone (XVII) was found to be much less labile in basic solution than is tetraacetic lactone (III). Thus, XVII can be retrieved from 1M KOH after 1 hr at 60°C, as can the *o*-methoxy derivative (XIX). When XVII is refluxed in 1M KOH for a hr, however, 3,5-dihydroxybiphenyl (XXIII) is isolated in 11% yield. Refluxing XVII in 1M methanolic KOH leads to a 67% yield of 2-carbomethoxy-3,5-dihydroxy-biphenyl (XXIV). 6-(2-Methoxy-phenacyl)-4-hydroxy-2-pyrone is destroyed under the latter conditions. The formation of XXIII and XXIV thus provides *in vitro* syntheses of biphenyls from a compound which is related to a plausible precursor in the biosynthesis of alternariol (XVIII) *viz.* (XXV).



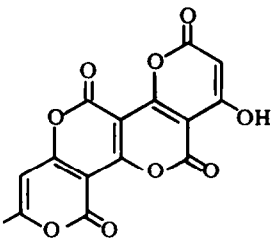
XXV



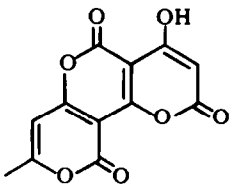
XXVI

So far all attempts to add a further pyrone ring to tetraacetic lactone III and to the esters XI have met with no success. Thus, reaction of III with malonyl dichloride in CF_3COOH gave only 3-acetyltetraacetic lactone (XIII: R = CH_3). Melting III with bis-(2,4-dichlorophenyl)-malonate gave a chlorine-containing compound which was not investigated further. The ester (XIII; R = C_2H_5) afforded 3'-acetyl-dipyrone (XIV) in 61% yield with malonyl dichloride in CF_3COOH and mixtures of XIV and dipyrone (V) when heated with bis-(2,4-dichlorophenyl)-malonate. No evidence was obtained for the formation of a 6-acetonyl-dipyrone derivative such as XXVI from any of these reactions.

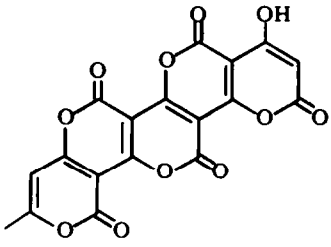
For the preparation of more extended poly-β-carbonyl progenitors e.g. "hexa-acetate" an extension of an earlier approach was adopted, our goal being the controlled hydrolysis of the tetrapyrone (XXVII).



XXVII

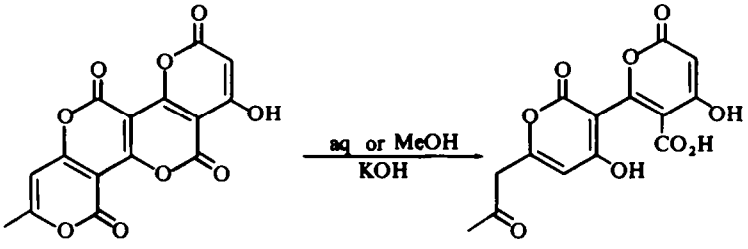


XXVIII



XXIX

The synthesis of the tetrapyrone (XXVII) was modified from the previous procedure[13] as follows. Brief treatment of dipyrone (V) with bis-(2,4-dichlorophenyl)-malonate at 265° afforded a separable mixture of dipyrone (60%), tripyrone (XXVIII) (20%), and tetrapyrone (XXVII) (2%) together with a small amount (0·04%) of the "heptaacetate-equivalent" pentapyrone (XXIX).

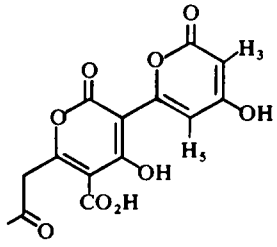


XXVII XXX

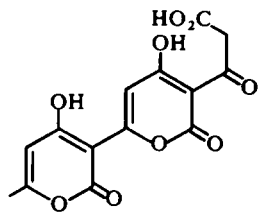
Contrary to our experience in the bi- and tri-cyclic series, treatment of the tetrapyrone (XXVII) with aqueous or methanolic KOH at room temperature (until no further change occurred in the UV spectrum of the solution) afforded a 9% yield of a crystalline *keto* acid (XXX) whose structure was assigned as follows: mass spectral and elemental analysis were consistent with the formula $C_{14}H_{10}O_9$ (M^+ 322) suggesting the hydrolysis of two pyrone rings and loss of one mole of CO_2. The presence of a carboxylic acid function was revealed in the infrared (ν_{max} 3580, 2700–2550, 1705 cm^{-1}) and by the reaction of XXX with bicarbonate, whilst the retention of the 4-hydroxy-2-pyrone chromophore followed from the IR (1720, 1635, 1560 cm^{-1}) and the characteristic mass spectral fragments at *m/e* 153, 126, 111 and 85.

The NMR spectrum of XXX in CF_3COOH showed a series of singlets at τ 7·60 (3H); 4·95 (2H); 3·96 (1H); 3·70 (1H), which, however, does not clearly differentiate between structures XXX–XXXIV, (R = CO_2H).

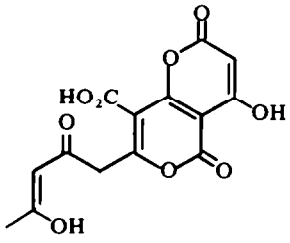
Structures XXXIII and XXXIV, (R = CO_2H) were rejected after examination of the UV spectrum of XXX which shows λ_{max} 223 and 307 nm. The latter maximum shifted in acid to 314 nm and in base to 290 nm. This behaviour is quite different from that of V[13] and XXXIV, (R = H)[19] which serve as models for XXXIII and XXXIV, (R = CO_2H) respectively. Structure XXXII seems most unlikely because of



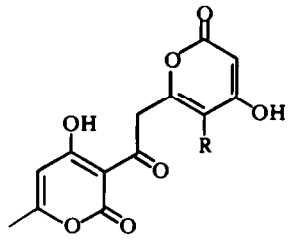
XXXI



XXXII



XXXIII



XXXIV

the reluctance of the acid to decarboxylate. Finally a choice in favour of XXX over XXXI was made by analysis of the vinylic proton pattern in the NMR. Structure XXXI would be expected to show the typical doublets of the 3 and 5 protons of the 4-hydroxy-2-pyrone system. Instead the vinylic protons are observed as singlets. Structure XXX thus corresponds to the selective hydrolysis of rings 1 and 3 of the tetracyclic structure, an observation which proved important in the development of the chemistry of the dipyrone (V). However. apart from *ca.* 10% recovered starting material, the remaining products proved intractable. Furthermore all attempts including base and acid treatment, irradiation, and pyrolysis to modify further the hexa-acetate progenitor (XXX) gave a similar mixture of intractable residues.

In view of the inaccessibility of XXVII and the ensuing poor yields of the partially hydrolysed structures (such as XXX) attention was directed to alternative syntheses of the masked poly-β-carbonyl array as described in the following papers.[14,20]

EXPERIMENTAL

Unless otherwise stated, UV spectra were measured in MeOH. λ_{max} values are given in nanometers. "λ_{max}(base)" implies that 1 M NaOH solution (1 drop) was added to the MeOH solution and the spectrum re-recorded. IR spectra were recorded using KBr discs. NMR spectra were recorded at 60 MHz (TMS). The parent ion in the mass spectra is recorded as M^+, together with other abundant ion peaks. TLC systems are designated thus: (A) 4:1 $CHCl_3$:AcOH; (B) 9:1 $CHCl_3$:AcOH; (C) 10:9:1 CCl_4:$CHCl_3$:AcOH and plates were visualized by means of iodine vapour and/or tetraazotized benzidine (TAB).

The action of aqueous sodium hydroxide on dipyrone (V). Dipyrone (V) (10 g) was vigorously shaken with 1M NaOH (200 ml) for 8 min, after which time most of the solid had dissolved to give a golden-green solution. The reaction mixture was filtered (removing undissolved dipyrone (500 mg) and the pH of the filtrate was adjusted to 3·5 with conc. HCl. A pale yellow precipitate (1·2 g) of dipyrone formed and was filtered.

The filtrate was saturated with NaCl and allowed to stand for 2 hr. The precipitate which formed was filtered off and dried *in vacuo* giving tetraacetic lactone-5-carboxylate (VII) (4·8 g). Recrystallization of VII

resulted in dehydration to dipyrone (V). The analytical sample had m.p. 280°C (begins to decompose with effervescence at 200°C). UV λ_{max} 280 (ε 3550); 255 (sh) (ε 7000); λ_{max} (base) 364, 275, IR (Nujol) ν_{max} 2700–2600 (w), 1730 (s), 1700 (s), 1690 (s), 1660 (s), 1570 (m) cm^{-1}. NMR (a) [5:1 $CDCl_3$:d_6-DMSO] 7·80, 3H(s); 5·95, 2H(s); 4·45, 1H(s); 0·00, 2H(br); (c) (TFA) 7·60, 3H(s); 5·69, 2H(s); 3·79, 1H(s). M.S. No M^+, *m/e* 194 (M^+—H_2O), 168 (M^+—CO_2), 153, 126, 111, 105, 85, 77, 69, 44, 43. TLC R_f 0·2 in 1:1 $CHCl_3$:AcOH; R_f 0·8 in 10:1:1 EtOH:AcOH:H_2O; orange with TAB. Colour fades rapidly to grey, then green and finally vanishes. Soluble in DMSO, AcOH, less so in H_2O, MeOH and dioxane. Insoluble in $CHCl_3$ and less-polar solvents. Dissolves freely with effervescence in $NaHCO_3$ solution. $FeCl_3$ test, red–brown complex. Analysis indicated progressive dehydration. ($C_9H_8O_6$ requires C, 51·0%; H, 3·8, Found: C, 52·2%; H, 3·92%). For satisfactory analysis the ethyl ester was prepared (*vide infra*). The filtrate after separation of acid (VII) was resaturated with NaCl and allowed to stand for a further 24 hr, whereupon a further precipitate formed. Filtration and recrystallization of this material from glacial AcOH gave 1·7 g of colourless, crystalline compound identical with an authentic sample of orsellinic acid (VI).

5-Carbomethoxy-tetraacetic lactone (XI; R = CH_3). Thionyl chloride (2·26 g, 0·019 M) (freshly distilled at 78–82°C) was dissolved in MeOH (50 ml). After cooling the solution to −10°C (ice-salt bath), N_2 was slowly bubbled through the stirred solution. Tetraacetic lactone-5-carboxylate (VII) (3·3 g, 0·0155 M) was added in small portions to saturation, keeping the temperature below −5°C. After complete addition (45 min) the reaction mixture was a thin, yellow paste. MeOH (10 ml) was added, the temperature raised to 40°C, the yellow solution stirred for a further 2 hr and the solvent evaporated *in vacuo* leaving a pale brown solid. This was dissolved in boiling C_6H_6 from which the product crystallized on cooling as straw coloured needles, m.p. 205–219°C (dec.). Crystalline structure changed from tiny prisms to long, thin needles at 165–172°C. UV λ_{max} 295–310 (br (ε 1500) 277 (sh) (ε 3500); 263 (ε 6500); λ_{max}(base) 320 (ε 4000); 269 (ε 10,500). IR ν_{max} 3450–3400 (br, w), 1740 (s), 1695 (s), 1575 (m) cm^{-1}. NMR ($CDCl_3$) 8·26, 3H(s); 6·85, 2H(q); J = 8 Hz (underwent about 50% exchange with 5% D_2O after one week); 6·57, 3H(s); 4·43, 1H(s); −0·73, 1H(s) (rapidly exchanged in 5% D_2O). High resolution M.S. M^+ 226·047696 *m/e* 198, 180, 166, 153, 142, 128, 127, 126, 99, 91, 85, 69, 44, 43. $C_{10}H_{10}O_6$ requires M^+ 226·047731 TLC (C) R_f 0·29.

5-Carbethoxy-tetraacetic lactone (XI; R = C_2H_5). Except for the substitution of absolute EtOH for MeOH, the procedure for the preparation of the 5-carbomethoxy derivative XI, (R = CH_3) was followed exactly, using thionyl chloride (1·28 g), acid (2·12 g) and alcohol (45 ml). A white solid (2 g) was obtained which recrystallized from C_6H_6 to give 1·8 g of fine white needles, m.p. 176°C (dec.). UV λ_{max} 285 (ε 2770); 256 (ε 6670). IR ν_{max} 3400 (br, w), 1730 (s), 1695 (s), 1570 (m) cm^{-1}. NMR ($CDCl_3$) 8·86, 3H(t); J = 7 Hz 8·28, 3H(s); 6·92, 2H(s); 6·30, 2H(q); J = 7 Hz 4·53; 1H(s); −0·65, 1H(s) (rapidly exchanged on addition of D_2O). M.S. M^+ 240 *m/e* 222, 194, 170, 166, 153, 152, 126, 99, 85, 69, 44, 43. TLC (i) acetone R_f 0·24; (ii) (A) R_f 0·28. Soluble in $CHCl_3$, less so in EtOH and C_6H_6. Insoluble in 10% $NaHCO_3$. $FeCl_3$ test: transient red complex. ($C_{11}H_{12}O_6$: (MW 240·2) requires C, 55·00; H, 5·04. Found: C, 55·24; H, 4·79%.) Yield: 75%.

Reaction of carboxylic acid with potassium hydroxide. Carboxylic acid (VII) (500 mg) was dissolved in 1M KOH aq (100 ml) and stirred under N_2. After 2 hr the reaction mixture was added to HCl and crushed ice. Extraction with EtOAc, drying over $MgSO_4$ and evaporation of solvent gave an oil, TLC showed five spots (including starting material) and chromatography over silica gel in $CHCl_3$ (followed by 1:50 MeOH in $CHCl_3$) afforded orcinol (10%) and orsellinic acid (10%) identical with authentic materials. The use of $Mg(OMe)_2$ as base resulted in formation of a salt from which (VII) could be regenerated.

Reaction of 5-carbethoxy-tetraacetic lactone (XI; R = C_2H_5) *with sodium hydride in dimethylsulphoxide.* A 60% dispersion of NaH in mineral oil (600 mg) was washed twice with dry C_6H_6 and DMSO (40 ml) was added. After the effervescence had ceased, a solution of ester (XI, R = C_2H_5) (1·12 g) in DMSO (25 ml) was added dropwise over 30 min to the rapidly stirred mixture. More gas was evolved and a series of colour changes from yellow green → crimson was observed during the next hour. The crimson solution was heated to 55° for a further hour after which time the colour changed to pale orange. The reaction mixture was added to conc. HCl and crushed ice and extracted with $CHCl_3$ (3 × 100 ml). The combined organic layers were shaken several times with Na_2CO_3 aq. The aqueous extract was acidified to pH 2 and extracted with ether (5 × 100 ml). The combined organic layers were dried (Na_2SO_4) and evaporated to give a brown powder (0·4 g). TLC (A) showed this to contain two compounds one of which did not move from the origin.

The powder was stirred with a $NaHCO_3$ solution and the insoluble material (300 mg) filtered off. This was shown to be almost pure dipyrone (V) by m.m.p., UV, NMR, mass spectrum and TLC.

The aqueous filtrate was acidified, saturated with salt and extracted with a large volume of EtOAc, evaporation of which gave tetraacetic lactone-5-carboxylate (VII) (80 mg). The course of this reaction was essentially the same when NaH and C_6H_6 were used.

Reactions of tetraacetic lactone-5-carboxylate (VII) *under decarboxylative conditions.* (i) *Slow pyrolysis in vacuo*—Acid VII (20 mg) was placed in a sublimation tube which was then plugged loosely with glass wool. The tube was evacuated to 0·1 mm and heated from room temperature to 150°C in a heating block. A yellow band formed on the cool part of the tube and after 30 min sublimation was complete. A product (2 mg) was collected and shown to be identical with dipyrone (V). A brown tar (12 mg) remained in the tube and was shown by TLC (A) to contain at least six compounds, including starting material, orcinol and orsellinic acid. The course of reaction was little changed either by the presence of Cu bronze or by preheating the sublimation block.

(ii) *Heating with copper bronze in quinoline*—Acid VII (200 mg) was dissolved in quinoline (15 ml), Cu bronze powder (20 mg) was added and the solution was stirred under N_2 in a flask heated in an oil bath at 120°C. The reaction was complete after 15 min (CO_2 trapped as $BaCO_3$).

The solution was cooled, filtered to remove the catalyst, poured into 100 ml of 2M HCl and extracted with 20 ml ether. The ethereal extract was washed with 20 ml portions of 2M HCl until the separated aqueous washing gave no white turbidity with 2M NaOH. The organic layer was washed twice more with acid, one with 10% $NaHCO_3$ and once with H_2O, filtered through NaCl and dried (Na_2SO_4).

After filtration and evaporation of the solvent, an oil (90 mg) was obtained. Separation by PLC (B) led to the isolation of orcinol (X) (60 mg). The same result was achieved using H_2O (pH 7) instead of quinoline. Heating in nitrobenzene yielded only intractable tars.

(iii) *Refluxing in water at* pH 5·5—Acid VII (146 mg) was dissolved in H_2O (5 ml) and M/100 HCl was added dropwise until the pH was 5·5. Cu bronze (18 mg) was added and the mixture refluxed.

After 1 hr the mixture was worked-up yielding a semi-crystalline solid (80 mg) recrystallized from EtOH as pale yellow needles identical with an authentic sample of dehydracetic acid (XII), m.p. and m. m.p. 108–109°C. UV λ_{max} 304, λ_{max} (base) 293. NMR ($CDCl_3$) 7·72, 3H(s); 7·33, 3H(s); 4·03, 1H(s).

Refluxing with copper bronze in dioxane—Acid VII (500 mg) and Cu bronze (50 mg) were added to dioxane (20 ml) which had been filtered through alumina. The reaction mixture was refluxed in a current of N_2 in an oil bath at 140°C. Evolution of CO_2 began after 5 min (complete after 3 hr). Filtration and evaporation of the solvent and evacuating to 0·1 mm yielded a brown tar (510 mg). This was taken up in 3 × 80 ml of boiling $CHCl_3$ and filtered onto a column of 50 g silica gel in $CHCl_3$. The insoluble residue (20 mg) was discarded. The column was eluted with $CHCl_3$ (1500 ml) (Fr 1), $CHCl_3$:MeOH 100:1 (Fr 2) (2600 ml) $CHCl_3$:MeOH 10:1 (500 ml) (Fr 3), collecting 50 ml fractions, which were examined by TLC (B) and combined yielding dehydracetic acid (XII) (18 mg) and dipyrone (V) (110 mg) (from Fr 1) and a compound (from Fr 2) which crystallized from $CHCl_3$–MeOH as straw-coloured needles (180 mg) (m.p. and m. m.p. with authentic tetraacetic lactone (III) (119–120°C) (second crop 110–117°)]. UV λ_{max} 284 (ε 8000); λ_{max} (base) 358 [(ε 2000) (decreasing on standing)]; 270 (ε 9000). IR ν_{max} 3350 (s), 1720 (s), 1675 (s), 1620 (m), 1570 (s) cm^{-1}. NMR (d_6-DMSO) 7·80, 3H(s); 6·23, 2H(s); 4·68, 1H(d), J = 2 Hz, 3·89, 1H(d), J = 2 Hz; ~2·2–0·0, 1H(b). M.S. M^+ 168 *m/e* 153, 140, 126, 111, 98, 87, 69, 55, 43. TLC (B) R_f 0·20. Dinitrophenylhydrazone: yellow needles from 1:1 EtOAc:ligroin, m.p. 197–199°C (dec.) (lit. 205–206°). M.S. M^+ 348. ($C_8H_8O_4.H_2O$ requires C, 51·61; H, 5·37. Found: C, 51·54; H, 5·38%). Yield: unreacted starting material 10%; dehydracetic acid, 4%; dipyrone, 23%; tetraacetic lactone, 38%.

Preparation of 3-acetyl-tetraacetic lactone (XIII, R = CH_3). Tetraacetic lactone (III; 89 mg), AcCl (0·5 ml) and CF_3COOH (2 ml) were refluxed under N_2 (oil bath) at 85–90°C for 2½ hr, after which time no more HCl was evolved, then poured onto 10 ml of crushed ice and HCl and allowed to stand for several hours. The solution was worked up as usual with EtOAc, yielding a brown oil which became a crystalline mass *in vacuo* (0·1 mm) at room temperature for several hours. Recrystallization from EtOAc:petroleum ether gave XIII, (R = CH_3) (40 mg) as colourless needles m.p. 88–91°C. UV λ_{max} 310; λ_{max} (base) 378, 284. NMR ($CDCl_3$) 7·72, 3H(s); 7·35, 3H(s); 6·42, 2H(s); 3·97, 1H(s); −4·92, 1H(s) (exchanged in D_2O). High resolution M.S. M^+ 210·052856 *m/e* 169, 168, 153, 126, 125, 111, 85, 98, 97, 69, 55, 43. $C_{10}H_{10}O_5$ requires M^+ 210·052817 TLC (C) R_f 0·14. Preparative TLC (B) yielded unreacted starting material (5 mg) and XIII, (R = CH_3) (5 mg). Yield 40%.

Reaction of 3-acetyltetraacetic lactone (XIII; R = CH_3) *with methanolic base.* (i) *At room temperature*—XIII (R = CH_3) (30 mg) was stirred under N_2 at room temperature in 0·5M NaOMe (5 ml) for 17 hr. Acidification and work-up as usual in $CHCl_3$ resulted in an 80% return of starting material.

(ii) *Under reflux conditions*—The starting material re-isolated from (i) above was refluxed in 0·5M NaOMe (5 ml) for 2 hr. No starting material remained and no products were isolated. TLC were streaky and gave no colours with DAB. No UV was obtained. It appeared that complete degradation had taken place.

3-Acetyl-4-hydroxy-6-phenacyl-α-pyrone (XIII; R = C_6H_5). A stirred suspension of freshly prepared $NaNH_2$ (0·6 mole) in liquid NH_3 was treated portionwise with dehydroacetic acid (XII) (33·6 g, 0·2 mole). After 1 hr a solution of methyl benzoate (13·6 g, 0·1 mole) in dry ether (50 ml) was added dropwise and the mixture then stirred for 90 min. The NH_3 was evaporated and the ice-cold brown residue decomposed with cold 2N HCl (500 ml). Ether (250 ml) was added to the mixture to dissolve unchanged dehydroacetic acid, and the product (12 g, 44%), m.p. 135° (lit.[17] 137–138°), was collected by filtation; a sample crystallized from EtOAc as pale yellow plates, m.p. 138°. The product gave no colour with methanolic $FeCl_3$.

The phenacyl pyrone (XIII; R = C_6H_5) (0·47 g) was quantitatively recovered after being kept in 1M KOH solution (50 ml) under N_2 for 2 hr followed by acidification. When the solution was boiled under reflux for 40 min no product was isolated. When a solution of the pyrone (1 g) in 1M methanolic NaOMe (50 ml) was boiled under reflux for 30 min the pyrone was recovered (90%) on acidification. The pyrone (1 g) was also recovered (50%) after being boiled under reflux in a solution of AcOH (10 ml) and concentrated HCl (10 ml).

4-Hydroxy-6-phenacyl-α-pyrone (XVII). (i) *From triacetic lactone and methyl benzoate*—A stirred suspension of freshly prepared $NaNH_2$ (0·2 mole) in liquid NH_3 (350 ml) was treated portionwise with triacetic lactone (II; R_1 = CH_3; R_2 = H) (12·6 g, 0·1 mole) the mixture became brownish-yellow and a light grey salt was deposited. After 1 hr a solution of methyl benzoate (13·6 g, 0·1 mole) in anhydrous ether (50 ml) was added dropwise, the mixture gradually darkened and the salt dissolved. After being stirred for a further 2 hr the mixture was decomposed with NH_4Cl (12 g) and the NH_3 boiled off; the residue was finally warmed under reduced pressure. The ice-cold residue was treated with 5N H_2SO_4 (500 ml), the product collected and washed with H_2O followed by petroleum (b.p. 40–60°). The white product (44%) had m.p. 174–176° (decomp.) and crystallized from EtOH to give the *pyrone* (XVII) as colourless elongated rhombs, m.p. 184–185° (decomp.) ν_{max} (Nujol) 3480 (OH), and 1695–1655 cm^{-1} (ketone and pyrone carbonyls unresolved). NMR (d_5-pyridine) 5·6 τ, 2H(s) (exchanged with D_2O); 4·52 τ 1H(d) J = 2 Hz; 3·62, 1H(d) J = 2 Hz; 1·33–2·83, 5H(m); −1·65, 1H(s) (exchanged in D_2O). (Found: C, 67·4; H, 4·3. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·4%).

(ii) *From the phenacyl pyrone* (XIII; R = C_6H_5)—The phenacyl pyrone (XIII; R = C_6H_5) (2·5 g) was added to stirred 90% H_2SO_4 (15 ml) at 130° under N_2. After 5 min the cooled blood-red solution was poured onto ice and the product (1·6 g, 76%), m.p. 166–170° (decomp.) collected. The product was suspended in boiling $CHCl_3$, filtered, and filtrate evaporated to low bulk to give the phenacyl pyrone (XVII) (0·3 g, 14%), m.p. 178–179° (decomp.), identical with the sample obtained under (i). The insoluble portion (0·8 g, 38%), m.p. 161–162° (decomp.), from the $CHCl_3$ washing was shown to be a polymorphic form of the pyrone XVII; its NMR, IR and UV spectra were identical with that of XVII although a m. m.p. was depressed with sintering at 137° and final decomposition at 163°. Compare similar results with the phenacyl pyrone (XIX).

4-Hydroxy-6(2-methoxy-phenacyl)-2-pyrone (XIX). This reaction was carried out on an 0·1M scale in the same way as described for the pyrone (XVII) except that methyl *o*-methoxybenzoate was added immediately after the triacetic lactone. The mixture was stirred for 1 hr before decomposition with NH_4Cl. The product (1 g, 4%) after crystallization from EtOH had m.p. 184° (decomp.) and was identified from its NMR spectrum (d_5-pyridine) 6·23 τ, 3H(s); 5·68 τ, 2H(s); 4·25 τ, 1H(d) J = 2 Hz; 3·65 τ, 1H(d) J = 2 Hz; 1·93–3·2, 4H(m), as the pyrone (XIX). (Found: C, 64·6; H, 4·6. $C_{14}H_{12}O_5$ requires C, 64·6; H, 4·6%).

From the aqueous acidic liquor a compound (1·2 g, 5%) slowly crystallized m.p. 158° (decomp.) whose NMR spectrum was identical to that of the pyrone XIX. A m. m.p. of this polymorphic form with XIX was 180° (decomp.) with darkening at 155°.

6-Methyl-4-oxo-3-salicylidene-2,3-dihydro-2-pyrone (XX). This reaction of triacetic lactone and salicylaldehyde was carried out in the same way as described for the pyrone (XVII). Some difficulty was experienced during the addition of the aldehyde due to the rapid formation of its ammonium salt or imine. The product (5 g, 22%) gave yellow plates from AcOH aq, m.p. 148–150°. ν_{max} ($CHCl_3$) 1735 (lactone carbonyl), and 1610 cm^{-1} (H-bonded unsaturated ketone carbonyl). NMR ($CDCl_3$): 7·79, 3H(s); 3·01, 1H(s); 2–2·83 τ, 5H(m). This product gives a deep red colour with methanolic $FeCl_3$. M.S. M^+ 230. It was recovered unchanged from 0·75M methanolic KOH aq after 16 hr. (Found: C, 68·0; H, 4·5. $C_{13}H_{10}O_4$ requires C, 67·8; H, 4·4%).

Mono-acetylation with acetic anhydride and pyridine. Tetraacetic lactone (III) (6 mg) was dissolved in acetic anhydride (2 ml) and dry pyridine (0·5 ml). After 10 min at room temperature, the solution was diluted with anhydrous C_6H_6 (10 ml) and evaporated *in vacuo* at room temperature. This was repeated twice more and the product recrystallized from EtOAc petroleum ether to give the enol acetate (XXI;

$R_1 = CH_3$; $R_2 = H$) as pale yellow needles, m.p. 150°C (dec.). UV λ_{max} 305 (ε 9000) (very broad absorption) (unaffected by addition of one drop of 1M acid); λ_{max} (base) 360, 272. After reacidification. λ_{max} 284. IR ν_{max} 1770(s) cm^{-1} NMR (19:1 $CDCl_3$:d_6-DMSO) 7·94, 3H(d); J = 0·9 Hz; 7·70, 3H(s); 4·60, 1H(d) J = 2 Hz; 4·33, 1H(q), J = 1 Hz; 3·97, 1H(d) J = 2 Hz; 2·00–2·70, 1H(br) (exchanged in D_2O). M.S. M^+ 210 *m/e* 168, 153, 126, 111, 98, 85, 69, 43.

Enol Acetate XXI, ($R_1 = C_6H_5$; $R_2 = CH_3CO$). A solution of the phenacyl pyrone XIII ($R = C_6H_5$) (1 g) in pyridine (5 ml) and acetic anhydride (5 ml) was kept at room temperature for 2½ hr and then poured onto crushed ice and dilute H_2SO_4. The product was crystallized from EtOH to give the enol *acetate* XXI, ($R_1 = C_6H_5$; $R_2 = CH_3CO$) (0·6 g, 52%) as orange elongated plates, m.p. 174–176°. NMR ($CDCl_3$) 7·48 τ, 3H(s); 7·32 τ, 3H(s); 4·06, 1H(s); 3·63, 1H(s); 2·26–2·69, 5H(m). (Found: C, 65·0; H, 4·5. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%). This compound was quantitatively recovered after being kept in 10% Na_2CO_3 solution for 10 min followed by acidification. In 5% NaOH solution it was rapidly hydrolysed to XIII, ($R = C_6H_5$). The enol acetate XXI, ($R_1 = C_6H_5$; $R_2 = H$) prepared as for XXI, ($R_1 = C_6H_5$; $R_2 = CH_3CO$) crystallized from AcOH as pale yellow needles, m.p. 213° (decomp.). ν_{max} (Nujol) 1765 (enol acetate carbonyl), and 1690 cm^{-1} (pyrone carbonyl). NMR (d_5-pyridine) 7·35 τ, 3H(s); 4·28, 1H(d) J = 2 Hz; 3·58, 1H(d) J = 2 Hz; 3·18, 1H(s); 2·08–2·32, 5H(m). (Found: C, 66·0; H, 4·6. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%).

Diacetate XXII. Tetraacetic lactone (III) (123 mg) was dissolved in dry pyridine (2 ml) and acetic anhydride (2 ml) and allowed to stand at room temperature for 1 hr. The solution was diluted with C_6H_6 and evaporated. This was repeated twice more and the resultant oil heated (water bath) (60°) (0·1 mm), subliming the diacetate (XXII) as pale yellow crystals (85 mg), m.p. 99–100°C. UV λ_{max} 328 (ε 9500); λ_{max} (base) 360, 270. After reacidification λ_{max} 284 (8000). IR 1775 (s), 1750 (s), 1660 (m), 1630 (m), 1555 (s) cm^{-1}. NMR ($CDCl_3$) 7·90, 3H(d), J = 0·9 Hz; 7·73, 3H(s); 7·68, 3H(s); 4·48, 1H(q), J = 1 Hz; 3·97, 1H(d), J = 2 Hz; 3·87, 1H(d) J = 2 Hz. M.S. M^+ 252 *m/e* 210 (M^+ —CH_2CO), 168 (M^+ —$2CH_2CO$). Freely soluble in $CHCl_3$ and Na_2CO_3 aq. ($C_{12}H_{12}O_6$ requires C, 57·14; H, 4·80. Found: C, 57·03; H, 4·71%).

3,5-*Dihydroxybiphenyl* (XXIII). A solution of the phenacyl pyrone (XVII) (1 g) in 1M KOH aq (20 ml) was refluxed for 1 hr (N_2). The cooled solution was poured onto ice and dilute H_2SO_4 to give a finely crystalline product (0·09 g, 11%), m.p. 157·5–159°. It crystallized from H_2O containing a little MeOH to give 3,5-dihydroxybiphenyl (XXIII) m.p. 159·5–160·5°, ν_{max} (Nujol) 3340 (OH), 1642 and 1610 cm^{-1} (aromatic C=C). NMR (d_6-acetone) 3·59, 1H(t) J = 2 Hz; 3·32, 2H(d) J = 2 Hz; 2·16–2·75, 5H(m), 1·76, 2H(s). M.S. M^+ 186. (Found: C, 76·9; H, 5·4. $C_{12}H_{10}O_2$ requires C, 77·4; H, 5·4%).

2-*Carboxymethyl*-3,5-*dihydroxybiphenyl* (XXIV). A solution of the pyrone (XVII) (1 g) in 1M methanolic NaOMe (20 ml) was refluxed for 30 min (N_2). The cooled solution was poured onto ice and dilute H_2SO_4 to give the biphenyl (XXIV) as white plates (0·7 g, 66%), m.p. 120–120·5°, a m. m.p. with an authentic sample[21] was 121–122°. This compound gives a pale brown colour with methanolic $FeCl_3$. NMR ($CDCl_3$) 6·56, 3H(s); 4·02, 1H(d) J = 2·5 Hz, 3·86, 1H(d) J = 2·5 Hz; 2·56–2·86, 5H(m).

The ester (0·1 g) was refluxed in 1M KOH (5 ml). Acidification of the cooled solution gave 3,5-dihydroxybiphenyl (XXIII) (50 mg, 66%), m.p. and m.m.p. 159–159·5°.

Reactions directed towards a synthesis of 6-*acetonyl-dipyrone* (XXVI). (i) *The reaction of tetraacetic lactone* (III) *with malonyl dichloride in trifluoroacetic acid*—A solution of tetraacetic lactone (237 mg) in TFA (2 ml) and malonyl dichloride (1 ml) was refluxed (N_2) for 8 hr (80–90°), when no more HCl was evolved and the mixture was allowed to cool to a brown tar which was triturated with ether and filtered. The solid residue was dissolved in boiling C_6H_6 and chromatographed on a silica gel column (30 g of adsorbent). 1:3 C_6H_6–$CHCl_3$ eluted 3-acetyl-tetraacetic lactone (XIII; R = CH_3) (50 mg) (17%). MeOH–$CHCl_3$ 1:19 eluted unreacted starting material (15 mg). Use of bis-(2,4-dichlorophenyl)-malonate instead of malonyl dichloride gave intractable tars.

(ii) *The reaction of* 5-*carbethoxy-tetracetic lactone* (XI; R = C_2H_5) *with malonyl dichloride in trifluoroacetic acid*—A solution of ester XI (R = C_2H_5) (385 mg) in TFA (2 ml) and malonyl dichloride (1 ml) was refluxed for 8 hr (N_2) (80°). The resultant brown tar was triturated with ether and a brown powder (322 mg) filtered off. It was sparingly soluble in cold $CHCl_3$ and was boiled in C_6H_6 (20 ml) and filtered onto a column (45 g of adsorbent). The C_6H_6 insoluble material was a pale grey powder shown to be identical with 3′-acetyl dipyrone (XIV) m.p. 244°C (dec); UV λ_{max} 345 (ε 2000); λ_{max} 374 (absorbance decreasing rapidly). NMR (TFA) 7·48, 3H(s); 7·17, 3H(s); 3·45, 1H(s). M.S. M^+ 236. TLC (B) R_f 0·43; highly fluorescent in UV light; no colour with TAB. $FeCl_3$ test negative.

Elution of the column with 10:1 $CHCl_3$–MeOH yielded more XIV. Yield of 3′-acetyl dipyrone 249 mg, 61%.

(iii) *Reaction of* 5-*carbethoxy-tetraacetic lactone* (XI; R = C_2H_5) *with bis-*(2,4-*dichlorophenyl*)-*malonate*—

Lactone (XI; R = C_2H_5) (1·2 g) and bis-(2, 4-dichlorophenyl)-malonate (3·94 g) were heated together for 7 min (250°), then cooled. Trituration of the resultant brown oil with ether gave a brown powder (0·9 g) and unreacted malonyl ester dissolved in the ether. The brown powder was dissolved in boiling $CHCl_3$ and eluted through a column (20 g of adsorbent) yielding first malonyl ester (450 mg), then dipyrone (V) (250 mg) and finally 3'-acetyl dipyrone (XIV) (100 mg). Overall yield of pyrones: 35%.

Tetrapyrone (XXVII)

Method 1—Dipyrone (V) (16 g) and bis-(2,4-dichlorophenyl)-malonate (45 g) were melted together (N_2) initially at 260–265°, maintained for 5 min, giving a dark brown tar which, after cooling, was triturated with ether (3 × 100 ml) to give a dark brown powder (30 g). This was stirred in boiling C_6H_6 (3 × 1 l) and the solution filtered onto a silica gel column (500 g). Elution with C_6H_6 removed unreacted ester. Elution with 1:3 C_6H_6:$CHCl_3$ gave successively unreacted dipyrone, a mixture of dipyrone and tripyrone (XXVIII), tripyrone and finally a mixture of tripyrone and tetrapyrone (XXVII) (15 l of eluant). Elution with $CHCl_3$ yielded more of this mixture, which could be separated by shaking with cold EtOAc and filtering. The residual solid thus obtained was tetrapyrone, identical with an authentic sample prepared from the reaction of tripyrone and bis-(2,4-dichlorophenyl)-malonate. A yellow, microcrystalline analytical sample was obtained by recrystallization from acetone. M.p. 280°C (dec.). UV λ_{max} 416 (sh) (ε 6000); 400 (ε 10,000); 385 (sh) (ε 9500); 286 (ε 5000); 273 (ε 4800). M.S. M^+ 330. (Calcd. for $C_{15}H_6O_9C$, 54·56; H, 1·83. Found: C, 54·71; H, 1·97%).

The C_6H_6 insoluble residue was stirred in boiling $CHCl_3$ and the solution obtained filtered onto a second column (30 g, of silica gel). Elution with $CHCl_3$ (4 l) gave a little more tetrapyrone (25 mg). Elution with 1:50 MeOH:$CHCl_3$ gave a brown powder (10 mg) with properties consistent with the assignment of the pentapyrone structure (XXIX). M.p. 300°C (decomp.) TLC (A) R_f 0·05; UV λ_{max} 412 (ε 10,000); 290 (sh) (ε 7000); 275 (ε 7100); 218 (ε 10,000); M.S. (very weak even at a source temperature of 260°C) M^+ 398 *m/e* 370, 330. $C_{18}H_6O_{11}$ requires 398. Total yield of tetrapyrone 520 mg (2%).

Method 2—An alternative separation technique was evolved to eliminate the tedious chromatographic procedure. The solid from the first ether trituration was refluxed in 1 l of C_6H_6 for 20 min, cooled to 50°C and filtered. The filtrate contained most of the di- and tripyrone present. The residue was refluxed in a further litre of C_6H_6 and cooled to room temperature. A precipitate of nearly pure tetrapyrone was formed. A third C_6H_6 treatment separated most of the remaining tetrapyrone. The pentapyrone could be separated from the residue by chromatography eluting with 1:50 MeOH:$CHCl_3$ as above. Yield 550 mg.

Base treatment of tetrapyrone. (i) *Action of aqueous potassium hydroxide*—Powdered tetrapyrone (XXVII) (502 mg) was added to 250 ml of stirred 1M KOH (N_2) at room temperature. After 30 min the solid had completely dissolved giving a red solution; after 4 hr no further change was observed in the UV spectrum of the basic solution, which was then acidified with 2M HCl.

The acidified solution was extracted eight times with 100 ml portions of $CHCl_3$ and the organic layer evaporated to half its original volume. A precipitate separated which was filtered off and dried to give 45 mg of the carboxylic acid (XXX). M.p. 163–169°C (with effervescence). UV: λ_{max} 307 (ε 16,000); addition of one drop of 2M HCl gave a bathochromic shift to 314 (ε 17,500); λ (base) 280 (ε 16,500). IR (Nujol): ν_{max} 3580 (m), 3350 (m), 2700–2550 (w), 1720 (s), 1705 (s), 1630 (s) cm^{-1}. NMR (TFA) 7·60, 3H(s); 4·95, 2H(s); 3·96, 1H(s); 3·70, 1H(s). M.S. M^+ 322 *m/e* 278 (M^+ –CO_2), 198, 153, 126, 111, 85. TLC (A) R_f 0·0. Sprays brown–orange in TAB. Soluble in 10% Na_2CO_3 with evolution of CO_2. Ferric chloride ($FeCl_3$) test: weak orange complex. ($C_{14}H_{10}O_9$ requires C, 52·18%; H, 3·13%. Found: C, 52·14; H, 3·21%). Yield 45 mg, 9%.

(ii) *Action of dry methanolic potassium hydroxide*—Tetrapyrone (378 mg) was added to 250 ml of stirred dry 1M methanolic KOH (N_2) at room temperature. The solid completely dissolved in 1 hr giving an orange solution. After 12 hr the mixture was cooled in ice-salt and acidified with conc. HCl. The precipitate formed was filtered off and the filtrate was diluted with H_2O and evaporated to half volume. After cooling, the mixture was worked up as usual with $CHCl_3$ giving 305 mg of orange tar, containing no starting material and mainly two products more polar than tetrapyrone.

To the tar was added a 1:1 mixture of ether and 10% $NaHCO_3$. The aqueous layer was separated, reacidified, worked-up as usual in $CHCl_3$ and examined on TLC. The chromatogram had now changed and was much more complex. None of the several spots gave a positive reaction to TAB spray. The neutral fractions were similarly complex and unaffected by TAB spray when examined on TLC and never was it possible to isolate enough pure material to make positive identifications of any of the components. Preparative TLC [Systems (A) and 1:1 $CHCl_3$:AcOH] was used to try to affect separation, but to no avail.

Similar results were obtained from reaction of tetrapyrone (XXVII) under a variety of basic, acidic and thermal conditions.

Treatment of acid XXX *with aqueous or methanolic potassium hydroxide.* Several attempts were made to further cleave and aromatise the acid formed from tetrapyrone. Conditions used were similar to those used for tetrapyrone cleavage and in all cases there was extensive degradation of the starting material and no pure product could be isolated.

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