Tetrahedron. Vol. 27. pp. 3039 to 3049. Pergamon Press 1971 Printed in Great Britain

BIOGENETIC-TYPE SYNTHESIS OF POLYKETIDES PART IX

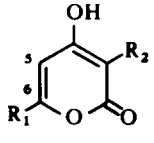
A MODEL FOR THE BIOSYNTHESIS OF 6-METHYL SALICYLIC ACID

A. I. SCOTT, H. GUILFORD and D. SKINGLE
(Kline Chemistry Laboratory, Yale University, New Haven, Conn. U.S.A.)

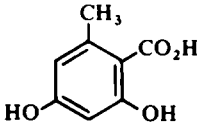
(*Received in USA* 5 *November* 1970; *Received for publication in the UK* 11 *January* 1971)

Abstract—An improved synthesis of tetraacetic lactone (TETAL) (VIII) is described. The reactions of pyrones (XIX) and of several derivatives of TETAL e.g. VI, VII are examined. Ring closure of VI after hydrolysis proceeds almost exclusively by aldol condensation. Hydrolysis of 5,6-dihydro TETAL (XXVIII; $R_1 = CH_3COCH_2$, $R_2 = H$) affords intermediates which serve as models for the biosynthesis of 6-methyl salicylic acid (IV).

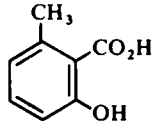
OUR search for further biogenetic analogies in the chemistry of poly-β-carbonyl systems e.g. I led us to examine in greater detail the 4-hydroxy-2-pyrone moiety (II) which had already[1,2,3] shown potential in the syntheses of acetate-malonate derived aromatic metabolites. For this purpose we were interested in establishing control over the mode of base-catalyzed intramolecular condensation. in extending the chain-length of the generated poly-β-keto chain and in producing analogies for the biosynthesis of metabolites related to orsellinic acid (III) but at a different oxidation level; in particular. 6-methyl-salicyclic acid (IV).



II

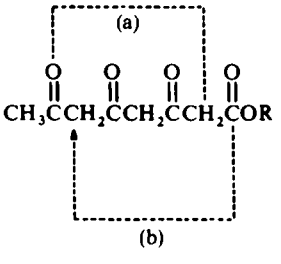


III



IV

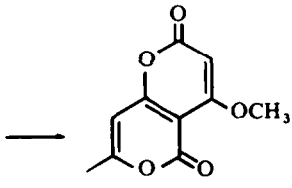
MOST studies of base catalyzed rearrangements of condensed 2-pyrone systems have led to products arising from intramolecular aldol-type condensation[1,2] (e.g. mode 1a).



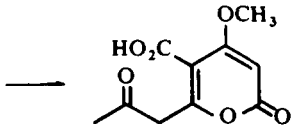
I

Success in achieving Claisen-type condensations from condensed pyrones (mode Ib) involved the use of a base in which the metal cation is capable of chelation viz. $Mg(OMe)_2$.[2,4,5,6] We next investigated the possibility that protection of the 4-hydroxy

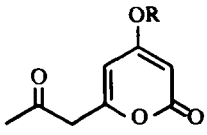
function as a methyl ether might prevent aldol condensation and thus promote the desired Claisen condensation. Accordingly the enol ethers V, VI and VII were prepared.



V

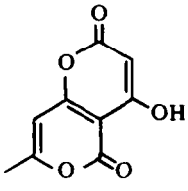


VI

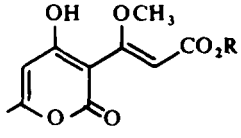


VII: R = CH_3
VIII: R = H

VII had already been reported by Bentley and Zwitkowits[7] as the product of CH_2N_2 treatment of tetraacetic lactone (VIII). Accumulation of large quantities of the latter material, however, either by Bentley's method[7] or by the procedure outlined in the preceding paper[3] involves both lengthy chromatography and mediocre yields. In fact a more satisfactory approach utilizes the readily available dipyrone (IX) as starting material.

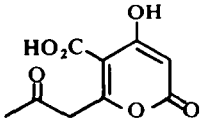


IX

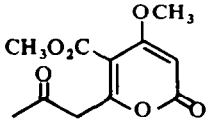


X

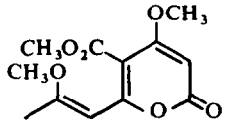
Thus, addition of ethereal methanolic CH_2N_2 to a dioxane solution of IX afforded the O-methyl dipyrone (V) m.p. 273° (d) in 82% yield. Partial hydrolysis of V by aqueous base furnished a monopyrone carboxylic acid, the structure of which is clearly VI rather than the alternative possibility (X; R = H) as shown by the NMR spectrum which displays singlets at 7·57, 5·87, 5·78 and 3·88 τ in the ratio of 3:3:2:1. Decarboxylation of the acid (VI) yielded tetraacetic lactone methyl ether (VII) m.p. and mixed m.p. 81–82°C, identical in every respect with a sample prepared from natural material according to Bentley's procedure.[7]



XI



XII



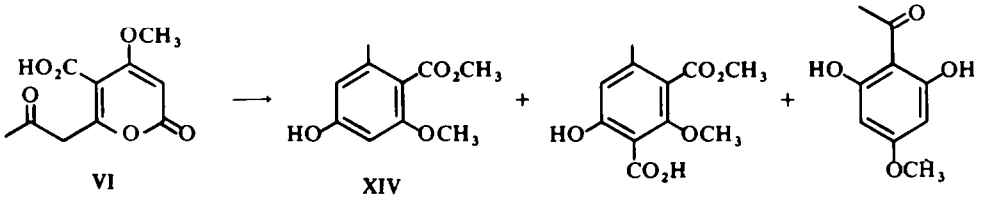
XIII

The spectroscopic and chemical properties of these compounds are consistent with the structural assignments; as in the case of the 4-hydroxy analogue (XI),[3] however, we were unable to obtain satisfactory combustion analysis data for the carboxylic acid (VI). Accordingly as a final proof of structure, the acid was esterified with CH_2N_2.

The methyl ester (XII) had the required mass spectrum (parent *m/e* 240), UV maxima at 279 and 240 nm (cf. VII λ_{max} 280 and 238 nm) and an empirical formula of $C_{11}H_{12}O_6$. The NMR spectrum displayed singlets at 7·77, 6·22, 6·19, 6·15 and 4·48 τ in the ratio of 3:2:3:3:1, data incompatible with the structure (X; R = CH_3).

Treatment of VI with excess CH_2N_2 forms the enol diether (XIII) while a solution of VI in H_2SO_4 regenerates the dipyrone (V). Demethylation of the enol ether (VII) with $AlCl_3$ in C_6H_6 affords tetraacetic lactone (VIII) m.p. and m.m.p. 119–120°C in 83% yield, thus providing a convenient alternative synthesis of this material.*

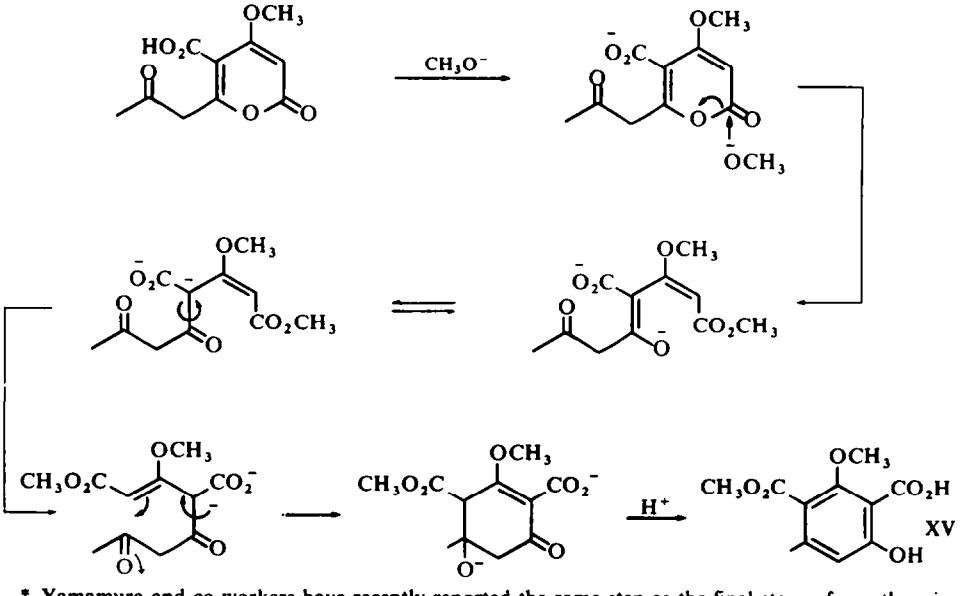
The acid (VI) was subjected to conditions which might be expected to favour intramolecular Claisen condensation. Thus with excess KOMe VI gave a mixture of three compounds (besides unreacted starting material). Two of these were isolated in sufficient quantity to allow definite identification as methyl 4-hydroxy-2-methoxy-6-methyl-benzoate (XIV) (28%) m.p. 112°C (lit. 114°C),[9] the methyl ester of the depside component iso-everninic acid,[10] and 3-carbomethoxyl-6-hydroxy-2-methoxy-4-methyl-benzoic acid (XV) (6%). This result was disappointing since neither of these



VI XIV XV XVI

compounds arise from a Claisen-type condensation. The formation of (XV) can be rationalised by the mechanism presented in Scheme 1, with decarboxylation at one of the intermediate or final stages leading to (XIV).

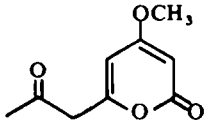
SCHEME 1



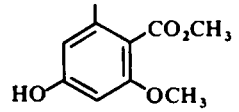
* Yamamura and co-workers have recently reported the same step as the final stage of an otherwise different synthesis.[8]

A third product (formed in about 1% yield) could not be obtained uncontaminated with XIV. Spectroscopic and other evidence (see experimental) suggests that this material is mainly 2,6-dihydroxy-4-methoxy-acetophenone (XVI) which corresponds to induction of Claisen-type condensation, albeit to a very minor extent. It is clear, however, that the major operative mechanism in this reaction again does not involve this kind of condensation and that protection of an appropriate ketone function as its enol ether is not necessarily a reliable means of selecting this particular mode of cyclisation.[11]

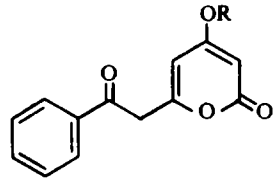
In a recent communication[12] Yamamura and coworkers reported that base catalysed rearrangement of O-methyl-tetraacetic lactone (VII) indeed affords 2,6-dihydroxy-4-methoxy-acetophenone (XVI). In our hands this reaction yielded solely methyl iso-everninate (XIV) although, as in many other examples of biogenetic-



VII



XIV

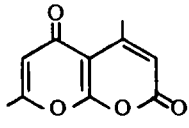


XVII

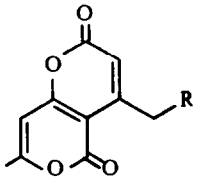
type synthesis, these different results are not mutually exclusive, since full experimental details of the Japanese work are not yet available.

In a cognate study the phenacyl enol ether (XVII; R = CH_3) was prepared by treatment of (XVII; R = H) with $(CH_3)_2SO_4$. In sharp contrast to the chemistry of (VII). (XVII; R = CH_3) can be recovered from 1 M KOH after 16 hr at room temperature or 40 min at 75° but is completely destroyed by 8 hr refluxing in 1M NaOMe.

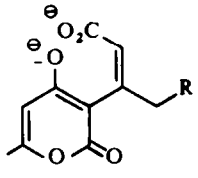
We now examined the problem of extending the potential poly-β-keto chain and to this end investigated some reactions of triacetic lactone (II; R_1 = CH_3, R_2 = H) with β-ketoesters. In 1907 Fleischmann reported the condensation of triacetic lactone with ethyl acetoacetate in the presence of HCl.[13] His suggested structure for



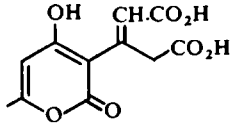
XVIII



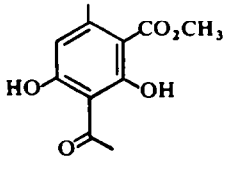
XIX



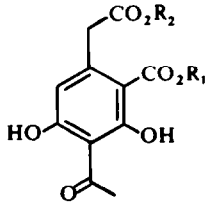
XX



XXI



XXII

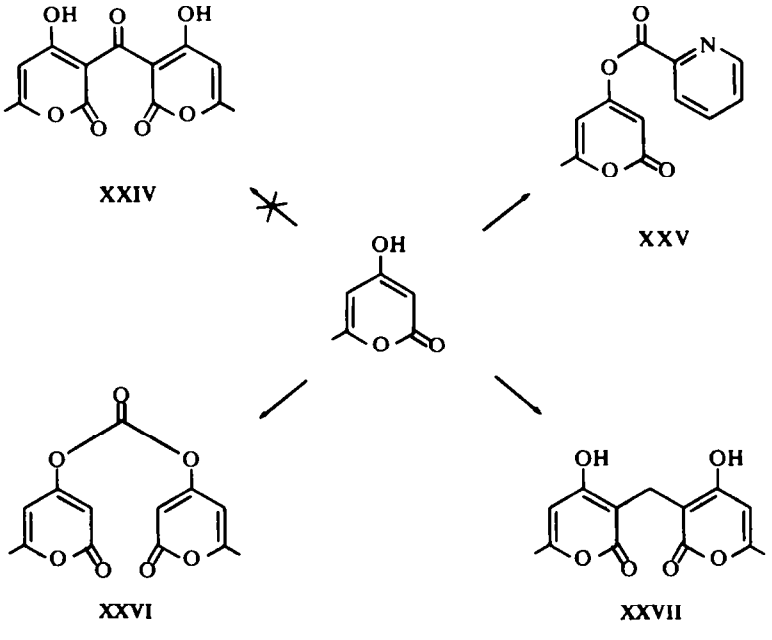


XXIII

the product was (XVIII) but this has recently been corrected to (XIX, R = H).[14,15] We have examined the reaction of triacetic lactone with both ethyl acetoacetate and dimethyl acetone dicarboxylate at 150° in the presence of pyridine and have found that the products are respectively Fleischmann's dipyrone (XIX; R = H) and the analogous compound (XIX; R = CO_2CH_3).

These compounds behave similarly under a variety of basic conditions: they are freely soluble in 5% NaOHaq, the anions (XX; R = H) and (XX; R = CO_2^-) presumably being generated. Acidification of the former regenerates (XIX; R = H) whilst the latter affords the dicarboxylic acid (XXI) which, on melting, is transformed to Fleischmann's dipyrone. Both XX (R = H) and XX (R = CO_2CH_3) rearrange to phenolic compounds in 5M NaOMe, the products being respectively methyl 3-acetyl-orsellinate (XXII)[16] and either (XXIII; R_1 = CH_3; R_2 = H) or (XXII; R_1 = H; R_2 = CH_3).

These reactions, although providing a source of oxygenated acetophenones, lacked the complete analogy for acyl phlorglucinol synthesis. The reaction of triacetic lactone with phosgene was also examined with a view to generating the potentially useful compound XXIV. In pyridine, however, triacetic lactone reacted with $COCl_2$ yielding the adduct XXV. With N,N-diethyl aniline in boiling toluene the product



XXIV XXV

XXVI XXVII

was the triacetic lactone carbonate (XXVI) but attempts to rearrange this with pyridine to the required product (XXIV) afforded only the adduct XXV. Jones' oxidation of 3,3'-methyl-bis-(triacetic lactone) (XXVII) proved to be unrewarding.[17]

In view of these unpromising results, we sought other methods of synthesizing poly-β-ketones (as reported in the following paper).[11] and examined the specific removal of one oxygen function in the synthesis of 6-methyl salicylic acid (6-MSA; IV).

Lynen and Tada have postulated[18] that the biosynthesis of 6-MSA involves

head-to-tail condensation of one acetate and two malonate units, a TPNH-dependent reduction followed by dehydration, condensation of a further malonate unit, aldol condensation and elimination of H_2O to give an enzyme-bond thiosalicylate moiety, hydrolysis of which liberates 6-methyl salicylic acid (IV). We felt that the 5,6-dihydro-4-hydroxy-2-pyrone template (XXVIII) might provide a useful model for study of

SCHEME 2

Proposed mechanism for the biosynthesis of 6-methylsalicylic acid

(1) $CH_3COSCoA + 2CH_2(COOH) - COSCoA \overset{E-SH}{\rightleftharpoons} CH_3COCH_2COCH_2CO{-}SE + 2CO_2$

(2) $CH_3COCH_2COCH_2CO{-}SE + NADPH + H^+ \rightarrow CH_3COCH_2CH(OH)CH_2CO{-}SE + NADP^+$

3,5 diketohexanoyl reductase

(3) $CH_3COCH_2CH(OH)CH_2CO{-}SE \rightleftharpoons CH_3COCH_2{-}\underset{trans}{CH{=}CH}{-}CO{-}SE$

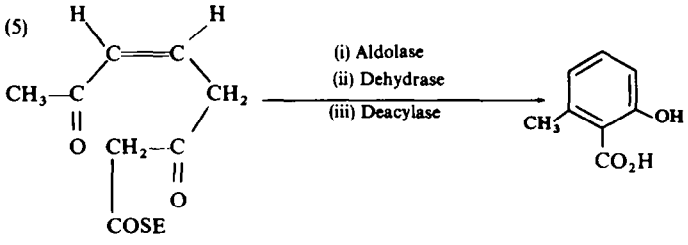
$\rightleftharpoons CH_3CO{-}\underset{cis}{CH{=}CH}{-}CH_2CO{-}SE$

β-hydroxy-5-ketohexanoyldehydrase/isomerase

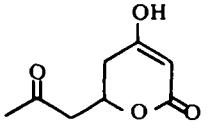
(4) $CH_3CO{-}\underset{cis}{CH{=}CH}{-}CH_2CO{-}SE + CH_2(COOH){-}COSCoA$

$\rightleftharpoons CH_3CO{-}\underset{cis}{CH{=}CH}{-}CH_2COCH_2CO{-}SE$

(5)



some of this putative scheme. Thus Bartels–Keith and Turner reported 5,6-dihydro-dehydroacetic acid to be the product of selective catalytic hydrogenation of the



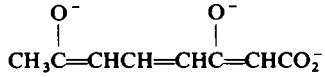
XXVIII

corresponding 2-pyrone (II, $R_1 = CH_3$; $R_2 = COCH_3$).[19] In model experiments it was found that Pd/C-catalyzed hydrogenation of triacetic lactone (II; $R_1 = CH_3$; $R_2 = H$), similarly affords 5,6-dihydro-triacetic lactone (II; $\Delta^{5:6}$ reduced; $R = CH_3$; $R_2 = H$)[20] m.p. 120–121° in 77% yield.

Extension of this method to the controlled reduction of tetraacetic lactone (VIII) gave 6-acetonyl-5,6-dihydro-4-hydroxy-2-pyrone (XXVIII) in 75% yield. The spectral

and chemical properties of this compound are in accord with the assigned structure: thus the UV absorption spectrum (λ_{max} 241 nm, ε 10,000) implies reduction of the $\Delta^{5,6}$-bond and correlates well with the observed data for 5,6-dihydrotriacetic lactone (λ_{max} 242, ε 12,000). Carbonyl frequencies in the IR spectrum at 1755 and 1730 cm^{-1} provide good evidence that the 2-pyrone chromophore has been destroyed and replaced by a 4-hydroxy-$\alpha\beta$-unsaturated δ-lactone (cf. 5,6-dihydrotriacetic lactone ν_{max} 1755 and 1720 cm^{-1}). This assignment is supported by the high resolution mass spectrum which shows the required parent ion together with fragmentation involving loss of 42 mass units (CH_2CO) followed by losses from *m/e* 128 reminiscent of the data for XXVIII, ($R_1 = CH_3$; $R_2 = H$).*

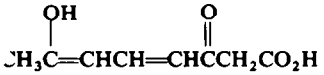
The behaviour of a methanolic solution of the reduced pyrone (XXVIII) on addition of 1M NaOH or NaOMe is dramatic: the colour of the solution becomes orange (λ_{max} 397 nm ε 50,000), due to the formation of the trianion (XXIX). Furthermore, acidification of this solution changes the absorption maximum to 295 nm. This value



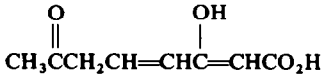
(XXIX)

correlates well with the calculated values for XXX and XXXI. Addition of further base regenerates the chromophore λ_{max} 397 nm.

If, however, the basic solution is stirred at room temperature for several hr and is



XXX λ_{max} 298 nm



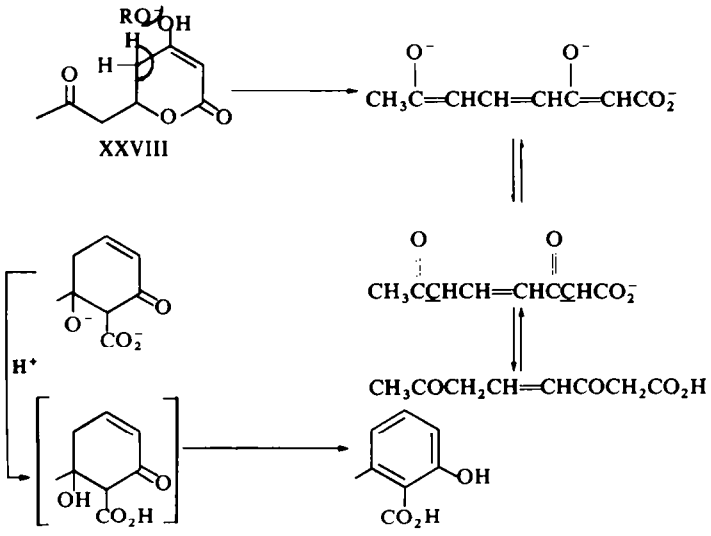
XXXI λ_{max} 288 nm

then acidified, the maximum absorption is observed at 310 nm. Addition of more base. does not regenerate the long chromophore, a hypsochromic shift to 295 nm being observed. The final acidified solution affords 6-methylsalicylic acid (IV) (28%) identical in every respect with authentic material.

In Scheme 3 is presented a mechanistic rational *e* for these observations.† The parallel with biosynthetic Scheme 2 of Lynen and Tada is remarkably close and provides an attractive model for the proposed biosynthesis. Attempts to isolate intermediates from this reaction with a view to relating them to the metabolic pathway have met with some preliminary success. Thus, brief treatment of 6-acetonyl-5,6-dihydro-4-hydroxy-2-pyrone with base followed by carefully controlled workup and TLC afforded a mixture of 6-MSA (λ_{max}^{base} 295 nm) and a new but uncharacterized, labile *intermediate* (λ_{max}^{base} 397 nm). Further base treatment of the mixture led to 6-MSA

* For comparative purposes we also examined the hydrogenation of 6-phenacyl-4-hydroxy-2-pyrone. In this case, however, the side-chain carbonyl is preferentially reduced. The resulting products are 6-phenethyl-4-hydroxy-2-pyrone m.p. 128° (lit. 137·5–138·5°)[21] (13%) and 6-(2-hydroxyphenethyl)-4-hydroxy-2-pyrone m.p. 143–144° (52%), identified by its spectra properties and its dehydration in conc. sulphuric acid to the known 4-hydroxy-6-styryl-2-pyrone.[5]

† No evidence was adduced for the formation of methyl 6-methylsalicylate. Hence we do not favour initial attack of methoxide at the lactone carbonyl.



SCHEME 3

only. The mixture was homogeneous on TLC and attempts to separate the components are in progress. The mass spectrum of the mixture has been examined but the major peaks are those of 6-MSA and no parent peak corresponding to the possible intermediates XXX or XXXI has been detected ($C_8H_{10}O_4$ requires M^+ 170). However the demonstration of an intermediate in this reaction is most promising. No definitive proof of the biosynthesis of 6-MSA will be forthcoming until the various precursors (e.g. as the N-acetyl-cysteamine esters) are tested as substrates in a cell-free enzyme preparation from a suitable microorganism such as *Penicillium patulum*. In the meantime the *in vitro* results described here provide indirect evidence that the postulates of Lynen and Tada are viable and encourage us to pursue a combined synthetic and biochemical approach which is now in hand.

EXPERIMENTAL

O-Methyl-dipyrone (V). To a solution of dipyrone (IX) (16·3 g) in dioxane (300 ml) cooled in an ice–salt bath was added excess ethereal methanolic CH_2N_2 (from 40 g of "diazald"). The white precipitate which had completely formed in 15 min was filtered, washed with ice-cold 2M HCl and with ice H_2O, dried over P_2O_5 and recrystallized from AcOH to give O-methyl dipyrone (V) (15·9 g) (82%) as white needles m.p. 270–273°C (dec.). UV λ_{max} 322–328 (ε 7720), 269 (ε 9980), λ_{max} (base) 394 (ε 6800), 311 (ε 6050). IR ν_{max} 1730, 1650, 1595, 1560. NMR (TFA) 7·50, 3H (s), 5·87, 3H (s), 3·96, 1H (s), 3·43, 1H (s). M.S. M^+ 208, TLC(B) R_f 0·71. $FeCl_3$ test: negative. ($C_{10}H_8O_5$ requires: C, 57·7; H, 3·87. Found: C, 58·04; H, 3·86%). From reactions of dipyrone (IX) with either $(CH_3)_2SO_4$ or MeI in the presence of K_2CO_3 was recovered quantitative amounts of starting material.

6-acetonyl-4-methoxy-2-pyrone-5-carboxylate (VI). A solution of O-methyl dipyrone (V) (0·64 g) in 1M NaOH (50 ml) was shaken vigorously for 20 min at room temperature. Acidification with 4M HCl (200 ml) at 0° afforded a white precipitate, filtered, dried *in vacuo* over P_2O_5 and recrystallized from EtOAc: ligroin yielding the carboxylic acid (VII) (0·56 g, 81%) as needles m.p. 81–83°; UV λ_{max} 283, 240 λ_{max} (base) 397, 285; IR ν_{max} 3520, 3400, 3150, 1710, 1610, 1540; NMR (TFA) 7·57, 3H (s); 5·87, 3H (s); 5·78, 2H (s); 3·88, 1H (s); MS M^+ 226 *m/e* 198, 184, 182, 140, 125. TLC (B) R_f 0·17 (yellow in TAB). $FeCl_3$ test negative. Freely soluble with effervescence in 10% $NaHCO_3$. ($C_{10}H_{10}O_6 \cdot H_2O$ requires: C, 49·19; H, 4·95. Found: C, 49·77; H, 4·93%).

Periodic examination of the NMR spectrum of the trifluoroacetic acid solution reveals that VI is completely dehydrated to dipyrone methyl ether (V) after four days under these conditions.

6-acetonyl-4-methoxy-2-pyrone (VII). (i) Carboxylic acid (VI) (30 mg) and Cu bronze (3 mg) were heated together at 160°C and 0·02 mm Hg in a sublimation apparatus for 10 min. Two fractions were collected: one (3 mg) identical with O-methyl dipyrone (V). The other was recrystallized from $CHCl_3$:ether affording 6-acetonyl-4-methoxy-2-pyrone (VII) (19 mg, 89%) m.p. and m.m.p. 81–83°C. $C_9H_{10}O_4$ requires: C, 59·34; H, 5·49. Found: C, 59·37; H, 5·56%.

(ii) 2-Pyrone carboxylic acid (VI) and Cu powder (40 mg) were heated together in quinoline (6 ml) at 150° for 15 min. The cooled, acidified mixture was extracted with $CHCl_3$ and washed with H_2O until the washings gave no turbidity with 1M NaOH. The dried $CHCl_3$ extract afforded tatraacetic lactone methyl ether (VII) (0·17 g, 80%).

6-Acetonyl-5-carbomethoxy-4-methoxy-2-pyrone (XII). To carboxylic acid (VI) 0·37 g) in MeOH (10 ml) was added ethereal CH_2N_2 until the solution was permanently green (5 min). The colour was dispersed with 2 drops of AcOH and the solvent evaporated affording a crystalline mass which was dissolved in $CHCl_3$ (20 ml) washed with $NaHCO_3$ (2 × 10 ml), H_2O (2 × 10 ml) and dried over $MgSO_4$. Evaporation and recrystallization of the residue from C_6H_6:ligroin gave 6-acetonyl-5-carbomethoxy-4-methoxy-2-pyrone (XII) (0·32 g, 82%) as needles m.p. 128–129°C. UV λ_{max} 279, (ε 3500), λ_{max} (base) 395, 312. IR ν_{max} 1720, 1705, 1610, 1535. NMR ($CDCl_3$) 7·77, 3H (s); 6·22, 2H (s); 6·19, 3H (s); 6·15, 3H (s); 4·48, 1H (s). MS M + 240 *m/e* 209, 198. TLC(C) R_f 0·15. $FeCl_3$ test: negative. ($C_{11}H_{12}O_6$ requires: C, 55·43; H, 5·16. Found: C, 55·2; H, 5·04%).

5-Carbomethoxy-4-methoxy-6-(2-methoxy-propenyl)-2-pyrone (XIII). To a solution of carboxylic acid (VI) (100 mg) in MeOH (10 ml) at 0°C was added excess ethereal CH_2N_2. After 1 hr a little AcOH was added and the solvents were evaporated leaving a yellow solid which recrystallized from MeOH affording the dienol ether (XIII) (56 mg, 50%) as pale yellow prisms m.p. 178–181°C. UV λ_{max} 332 (ε 7200) 249 (unaffected by acid or base). IR ($CHCl_3$) ν_{max} 1730, 1715, 1630, 1595. NMR ($CDCl_3$) 7·64, 3H (s); 6·32, 3H (s); 6·13, 3H (s); 6·11, 3H (s); 4·58, 1H (s); 4·38, 1H (s) (unaffected by NaOD). MS M$^+$ 254·079261 ($C_{12}H_{14}O_4$ requires M$^+$ 254·079130). TLC (C) R_f 0·29. $FeCl_3$ test: negative.

Tetraacetic lactone (VIII). A solution of 6-acetonyl-4-methoxy-2-pyrone (VII) (145 mg) in warm C_6H_6 (10 ml) was refluxed with $AlCl_3$ (600 mg) for 2 hr. Evaporation of the solvent and decomposition of the complex with 2M HCl at −5°C afforded a yellow powder. Solid $NaHCO_3$ was added adjusting the pH to 3·5 and the mixture was diluted with H_2O to 100 ml. Extraction with EtOAc (3 × 20 ml) and recrystallization of the crude product from $CHCl_3$:MeOH yield tetraacetic lactone (VIII) (111 mg, 83%) m.p. and m.m.p. 119–120°C.

Reaction of carboxylic acid (VI) *with* 1M *methanolic potassium hydroxide.* Acid (VI) (1·14 g) was refluxed under N_2 in 1M KOMe (100 ml) for 2 hr, cooled and acidified by dropwise addition of concentrated HCl at −10°C. KCl was filtered off, washed with MeOH and the filtrate evaporated to an oil. Taken up in $CHCl_3$, washed with H_2O, dried and evaporated giving an amorphous solid (0·6 g). Preparative TLC (B) afforded four components which were, in order of increasing R_f:

(i) Unreacted starting material (VI) (70 mg, 6%).

(ii) Methyl 4-hydroxy-2-methoxy-6-methyl-benzoate (XIV) (270 mg, 27%) colourless needles from ether at −17°C, m.p. 112°C (lit. 114°) UV λ_{max} 283 (ε 2860), 250 (ε 4600), λ_{max} (base), 295 (ε 9000). IR ν_{max} 3500–3250, 1710, 1690, 1615, 1570, 1120, 830. NMR ($CDCl_3$) 7·78, 3H (s); 6·30, 3H (s); 6·12, 3H (s); 4·67–3·17, 1H (br); 3·77, 2H (s). MS M$^+$ 196 TLC (B) R_f 0·37, vermilion in TAB. $FeCl_3$ test: deep purple complex. Gibbs' test: negative. Soluble in NaOH, insoluble in $NaHCO_3$. ($C_{10}H_{12}O_4$ requires: C, 61·2%; H, 6·1. Found: C, 61·28; H, 6·13%).

(iii) 2,6-Dihydroxy-4-methoxy-acetophenone (XVI) tentative structural assignment). Isolated 20 mg of material not free of (XIV). UV λ_{max} 325 (sh), 283, 240. λ_{max} (base) 345–355 (sh), 320, 290. NMR ($CDCl_3$) 7·33, 3H (s); 6·26, 3H (s); 4·05. MS M$^+$ 182. TLC (B) R_f 0·44, orange in TAB.

(iv) 3-carbomethoxy-6-hydroxy-2-methoxy-4-methyl-benzolic acid (XV) (75 mg, 6%) colourless needles from EtOAc: petroleum ether, m.p. 110–111°C. UV λ_{max} 298 (ε 2500) λ_{max} (base) 295 (ε 5800). IR ν_{max} 3450, 3100, 2650, 1736, 1645, 1610, 1565 cm^{-1}. NMR ($CDCl_3$) 7·68, 3H (s); 6·32, 3H(s), 6·00, 3H (s); 3·28, 1H (s); -4-2, 2H (br). MS M$^+$ 240. TLC (B) R_f 0·63. $FeCl_3$ test: deep purple complex. Gibbs' test: negative. Freely soluble in $NaHCO_3$ with effervescence. ($C_{11}H_{12}O_6$ requires: C, 55·43; H, 5·16. Found: C, 55·40; H, 5·14%).

4-Methoxy-6-phenacyl-2-pyrone (XVII; R = CH_3). 4-Hydroxy-6-phenacyl-2-pyrone (XVII; R = H) (1·15 g), anhyd K_2CO_3 (1 g) and $(CH_3)_2SO_4$ (0·5 ml) were stirred for 3 hr in acetone (50 ml) at room temperature. The mixture was evaporated to dryness and ice-cold 4M H_2SO_4 (40 ml) added, precipitating a

product which was washed thoroughly with H_2O and crystallized from C_6H_6 affording the 4-methyl ether (XVII; R = CH_3) (0·45 g, 37%) as colourless rhombs m.p. 137–138°C (0·35 g of starting material also recovered). NMR ($CDCl_3$) 6·19, 3H (s); 5·67, 2H (s); 4·52, 1H (d). J = 2·5 Hz, 3·96, 1H (d) J = 2·5 Hz, 2·66–1·9 τ 5H (m). MS M^+ 244. ($C_{14}H_{12}O_4$ requires: C, 68·8; H, 4·9. Found: C, 69·2; H, 5·0%). This compound (1 g) was recovered after being kept in 1M KOH (25 ml) under N_2 at room temperature for 16 hr, or at 75°C for 40 min, but was mostly destroyed after refluxing in 1M NaOMe in MeOH (25 ml) for 8 hr.

4,7-Dimethylpyrano(4,3-b)*pyran-2,5-dione* (XIX; R = H). Triacetic lactone (10 g, 0·079 mole), ethyl acetoacetate (25 ml, 0·2 mole), and pyridine (6 drops) were heated at 150° in a distillation apparatus. The triacetic lactone gradually dissolved with evolution of gas to form a clear yellow solution, and after the mixture was cooled and the crystalline mass treated with CCl_4. The product was washed with CCl_4 to give 4,7-dimethylpyrano[4,3-b]pyran-2,5-dione (6·7 g, 44%) as pale yellow needles, m.p. 210–213°. Crystals from $CHCl_3$ as white needles, m.p. 216–217° (lit. 215–216°). NMR ($CDCl_3$) 7·65, 3H (d); J = 0·8 Hz; 7·44, 3H (d) J = 1·2 Hz; 3·92, 1H (q) J = 1·2 Hz; 3·81, 1H (q) J = 0·8 Hz.

When boiled for 2 hr with 10% NaOH aq this product (1 g) was recovered (0·7 g), m.p. and m.m.p. 213–215°, on acidification. This compound (0·8 g) was quantitatively recovered after being heated under reflux with 2N H_2SO_4 (25 ml) and MeOH (15 ml) for 90 min.

4-Carbomethoxymethyl-7-methylpyrano[4,3-b]*pyran-2,5-dione* (XIX; R = CO_2CH_3). This compound was prepared from triacetic lactone (3·15 g, 0·025 mole) and dimethyl acetone dicarboxylate (7 ml) as for compound (XIX; R = H). The product crystallized from C_6H_6 and then $CHCl_3$ to give colourless elongated rhombs (1 g, 16%) m.p. 190–191°. NMR ($CDCl_3$) 7·78, 3H (d) J = 0·7 Hz; 6·25, 3H (s); 6·11, 2H (bs); 3·89, 1H (t) J = 0·7 Hz; 3·78, 1H (q); J = 0·8 Hz. Mass spectrum M^+ 250. ($C_{12}H_{10}O_6$ requires: C, 57·6; H, 4·01. Found: C, 57·55; H, 4·03%)

Hydrolysis of 4-carbomethoxymethyl-7-methylpyrano[4,3-b]*pyran-2,5-dione.* The ester (1 g) was warmed on the steam-bath for 1 hr with 5% NaOH aq (20 ml). The cooled solution was poured onto ice and dilute H_2SO_4. After 24 hr the acid (XXI) was deposited as elongated pale yellow rhombs (0·8 g, 79%), m.p. 199° (dec.). NMR (d_1-TFA) 7·53, 3H (d) J = 0·8 Hz; 5·83, 2H (bs); 3·49, 1H (t) J = 0·8 Hz; 3·43, 1H (q) J = 0·8 Hz. The solidified melt remelted at 215–217° and was identified by mixture m.p. as 4,7-dimethylpyrano-[4·3-b]pyran-2,5-dione. For analysis XXI was crystallized from EtOH aq. (Found: C, 51·7; H, 3·8. $C_{11}H_{10}O_7$ requires: C, 52·0; H, 4·0%).

Methyl 3-acetylorsellinate (XXII). A solution of 4,7-dimethylpyrano[4,3-b]pyran-2,5-dione (1 g) (XIX; R = H) in NaOMe/MeOH (prepared from 25 ml MeOH and 3 g Na) was refluxed for 30 min (N_2). The cooled solution was poured onto crushed ice and AcOH and the buff-coloured product (0·2 g, 17%) m.p. 97–98·5°, collected. It crystallized from petroleum ether (b.p. 60–80°) as colourless needles, m.p. 100° (lit.[16] 101°), which gave a magenta colour with $FeCl_3$/MeOH; ν_{max} ($CHCl_3$) 1625 cm^{-1}, (ester and ketone H-bonded carbonyls unresolved). NMR ($CDCl_3$) 7·54, 3H (s); 7·29, 3H (s); 6·06, 3H (s), 3·73, 1H (s). MS M^+ 224. (Found: C, 58·6; H, 5·6. $C_{11}H_{12}O_5$ requires: C, 58·9; H, 5·4%).

Reaction of 4-carbomethoxymethyl-7-methylpyrano[4,3-b]*pyran-2,5-dione* (XIX; R = CO_2CH_3) *with sodium methoxide.* A solution of the ester (0·9 g) in NaOMe/MeOH (2·7 g Na, 25 ml MeOH) was boiled under reflux for 40 min (N_2). The cooled solution was poured onto ice and AcOH, the product collected and crystallized from C_6H_6:EtOA to give a microcrystalline material (0·1 g), m.p. 205–207° (dec), ν_{max} (nujol) 1710 and 1650 cm^{-1}. NMR (d_5-pyridine) 7·28, 3H (s); 6·09, 3H (s); 5·88, 2H (s); 3·3, 1H (s), −2·75, 1H (s). MS M^+ 268. This product was soluble in $NaHCO_3$ aq but insoluble in H_2O. It gave a reddish-magenta colour with methanol ferric chloride.

These properties are consistent with the structure (XXIII; R_1, R_2 = H, CH_3).

Reaction of triacetic lactone with phosgene and pyridine. A solution of triacetic lactone (3·15 g, 0·025 mole) in pyridine (30 ml) was treated with $COCl_2$ until a gain in weight of 1·25 g (0·0125 mole) was obtained. The solution gradually darkened with slight warming and a buff-coloured solid was deposited. The mixture was left overnight, then treated with dilute HCl and the product (2 g, 35%) decomposed 265°, collected and washed thoroughly with dilute HCl and H_2O affording a compound identical (m.p., IR) with the sample obtained from the carbonate of triacetic lactone. It crystallized from EtOH acetone to give (XXV) as fine white needles, decomp. 267°. UV λ_{max} 281 log ε 4·05. IR ν_{max} ($CHCl_3$) 1725 cm^{-1}. NMR (TFA) 7·6, 3H (m); 4·8, 1H (s) 4·0–3·67, 4H (m); 3·09–2·92, 1H (m). When this product (1 g) was suspended in MeOH, treated with 10% Na_2CO_3 aq (4 ml) and warmed on the steam-bath, a deep amber solution was obtained smelling strongly of pyridine. The compound dissolves in methanolic NH_3 to give after evaporation an oily residue smelling strongly of pyridine.

Triacetic lactone carbonate (XXVI). A suspension of triacetic lactone (2·5 g, 0·02 mole) in boiling toluene

(150 ml) containing N,N-diethylaniline (3·5 ml) was aspirated with $COCl_2$ until a clear amber solution was obtained (30 min). The cooling solution was then aspirated with N_2 to remove phosgene. Evaporation of the solution under reduced pressure gave the crude carbonate (1·8 g) m.p. 133° after being washed with H_2O. It crystallized from C_6H_6 to give white plates, m.p. 138°, ν_{max} (Nujol) 1805 and 1710 cm^{-1}, λ_{max} 286 mμ (log ε 4·14). NMR ($CDCl_3$, 7·69, 6H (m); 3·87, 2H (m); 3·79, 2H (m). ($C_{13}H_{10}O_7$ requires: C, 56·1; H, 3·6. Found: C, 56·0; H, 3·5%).

When this carbonate (0·317 g) was dissolved in pyridine (2 ml) crystals separated. After 30 min the mixture was diluted with CCl_4 and the product (0·17 g, 79%) washed with CCl_4. This compound decomp. 265°, was identified (m.p. IR) as the pyridine carboxylic ester (XXV).

5,6-*Dihydro-triacetic lactone.* A solution of triacetic lactone (1·26 g) in EtOAc (350 ml) was hydrogenated in the presence of 10% Pd/C (0·27 g). After 24 h the uptake of H_2 was 1 mole equivalent. Filtration through Celite 545, evaporation of the solvent and crystallization from EtOH gave 5,6-dihydro-triacetic lactone (1·06 g, 77%) m.p. 120–121°C (lit. 124°). (C_6H_8: requires: C, 56·25; H, 6·25. Found: C, 56·1; H, 6·23%).

6-*Acetonyl*-5,6-*dihydro*-4-*hydroxy*-2-*pyrone* (XXVIII). Tetraacetic lactone (VIII) (330 mg) was hydrogenated in MeOH solution as described for triacetic lactone affording (XXVIII), (244 mg, 75%) m.p. 128–129°. UV λ_{max} 242 (ε, 10000) λ_{max} (base) 398 (ε 50000). IR 3400, 1755, 1730. MS M^+ 170·05775 ($C_8H_{10}O_4$ requires: M^+ 170·057703). TLC R_f 0·4 (A).

6-*Methyl-salicylic acid* (V). 6-Acetonyl-5,6-dihydro-4-hydroxy-2-pyrone (0·2 g) was stirred in 1M KOH under N_2 at room temperature for 36 hr. Acidification with 4M HCl (0°), extraction with $CHCl_3$ and separation on TLC afforded 6-methyl-salicylic acid (50 mg, 28%) identical with authentic material.

Hydrogenation of 6-*phenacyl*-4-*hydroxy*-2-*pyrone.* Catalytic hydrogenation of this compound (0·7 g) (as outlined for triacetic lactone) afforded:

(i) 6-phenethyl-4-hydroxy-2-pyrone (50 mg, 13%) as colourless needles from ether, m.p. 137°C (lit 137·5–138·5°C. UV λ_{max} 282 (ε 7000). NMR ($CDCl_3$) 7·18, 4H (m); 4·47, 1H J = 2 Hz; 4·27, 1H (d) J = 2 Hz, 5–4 1H (br); 2·75, 5H (bs). MS M^+ 216. TLC (A) 0·58.

(ii) 6-(2-Hydroxyphenethyl)-4-hydroxy-2-pyrone (360 mg, 52%) as white prisms m.p. 143–144° from ether:$CHCl_3$. UV λ_{max} 284 (ε 6800). NMR (d_6-acetone 7·15, 2H(d) J = 7 Hz; 4·89, 1H (t) J = 7 Hz; 4·64, 1H (d) J = 2 Hz; 4·00, 1H (bs); 2·62, 5H (m). TLC (A) R_f 0·3. ($C_{13}H_{12}O_4$ requires: C, 67·3; H, 7·90. Found: C, 67·1; H, 7·87%). This material is unaffected by 1M NaOH after one week at room temperature, does not form a 2,4-dinitrophenylhydrazone and after 1 hr in 0·5 ml of conc. H_2SO_4 is converted to 4-hydroxy-6-styryl-2-pyrone m.p. 232–245°C (dec.), identical with an authentic sample.[5]

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