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PYRONE STUDIES—I†

BIOGENETIC-TYPE SYNTHESIS OF PHENOLIC COMPOUNDS

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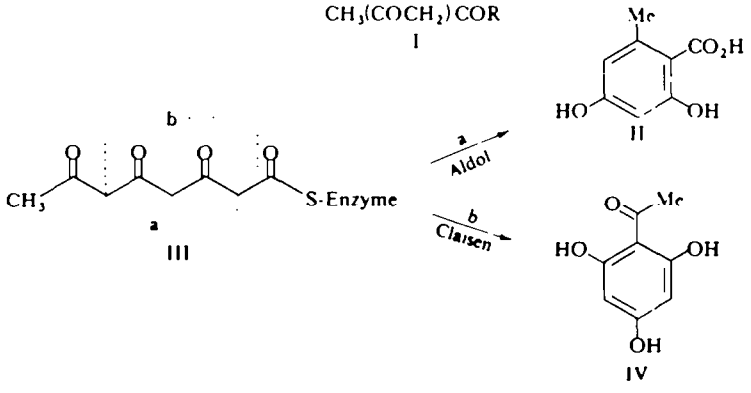
Abstract—A general solution is provided to the problem of synthesizing linear chains of poly-β-carbonyl function and their successive condensation to aromatic compounds.

INTRODUCTION

THE first suggestion that head-to-tail condensation of acetic acid units could account for the biosynthesis of certain classes of aromatic compounds was made in 1907.[1] These considerations were based upon the reactivity of synthetic linear β-polyketones (as I; n ≯ 2) which underwent condensation of the aldol type in basic solution to form aromatic phenolic compounds reminiscent of structural types found in Nature.

Similar ideas were adduced by Robinson[2] but, in the absence of experimental support, remained for many years simply as interesting speculations. By extrapolating the known biochemical data on fatty acid biosynthesis, Birch in 1953[3,4] independently rediscovered Collie's hypothesis and laid the experimental basis of the biochemical



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† Preliminary Communication, *J. Am. Chem. Soc.* **87**, 3004 (1965).

[1] J. N. Collie, *J. Chem. Soc.* **91**, 1806 (1907); *Proc. Chem. Soc.* 230 (1907).

[2] R. Robinson, *Structural Relations of Natural Products* Clarendon, Oxford (1955).

[3] A. J. Birch and F. W. Donovan, *Austral. J. Chem.* **36**, 360 (1953).

[4] A. J. Birch, *Proc. Chem. Soc.* 3 and Refs cited (1962).

"acetate" route to aromatic compounds. Further studies[5-9] have been summarized by Birch[4] and by Lynen[10,11] whose unifying "multi-enzyme complex" theory rationalizes the known biochemical steps where a starting acetyl coenzyme unit detaches successive units of enzyme-bound malonate in fatty acid biosynthesis.

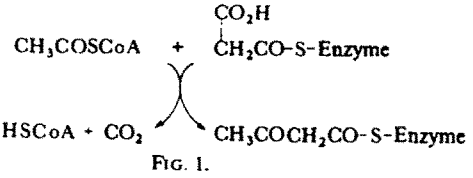
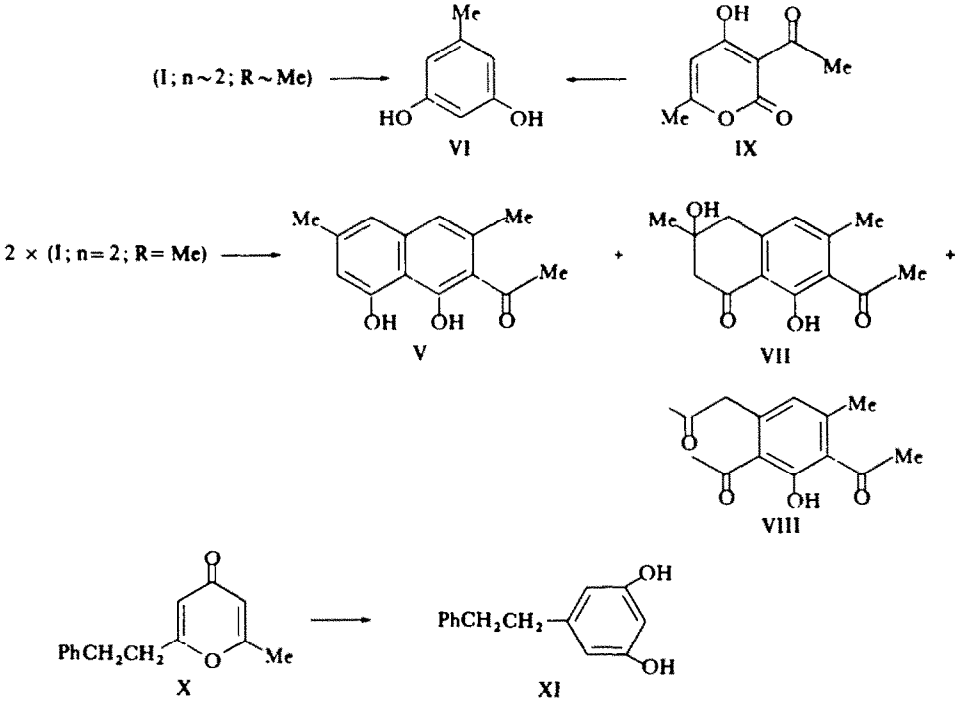


FIG. 1.

Extension can be made to the production of aromatic compounds such as 6-methylsalicylic acid or orsellinic acid (II) via the (hypothetical) β-tetraketone (III) chain.[12]



[5] J. D. Bu'Lock, H. M. Smalley and G. N. Smith, *Proc. Chem. Soc.* 209 (1961); *J. Biol. Chem.* 237, 1778 (1962).

[6] D. C. Allport and J. D. Bu'Lock, *J. Chem. Soc.* 4090 (1958); 654 (1960).

[7] Review: S. W. Tanenbaum in *Biogenesis of Antibiotic Substances* Ch. 12. Academic Press, New York (1965).

[8] G. Ehrensvard in XVIIIth *Congress of Pure and Applied Chemistry* 1959. (Plenary Lectures) Butterworths, London (1961).

[9] Review: S. Gatenbeck in *Biogenesis of Antibiotic Substances* Ch. 19. Academic Press, New York (1965).

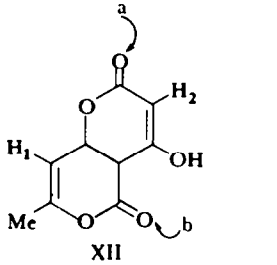
[10] F. Lynen and M. Tada, *Angew. Chem.* 73, 513 (1961).

[11] F. Lynen, *Fed. Proc.* 20, 941 (1961).

[12] cf. J. W. Richards and J. B. Hendrickson, *Biosynthesis of Terpenes, Steroids and Acetogenins* Ch. 1–5. Benjamin, New York (1964).

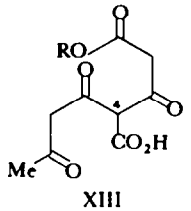
Our main objective has been to devise a general synthesis of β-polyketo acid chains of varying length and to convert these to aromatic compounds of natural type. Inherent in such a complete solution would be the control of aldol (type a) or Claisen (type b) condensation (III → II or IV). At the outset of our investigations the literature contained reports[13-15,22] describing the conversion of protected and unprotected β-polyketones to aromatic compounds. The classical examples were provided by the work of Collie[13,14] who succeeded in converting dehydroacetic acid (IX) (a protected β-triketone) to orcinol (VI) under alkaline conditions. Similar treatment of heptane-2,4,6-trione (I; n = 2; *R* = Me) yielded orcinol and three other aromatic compounds whose structures have been established[14,14a,15] as V, VII and VIII. The latter compounds clearly arise by intermolecular condensation of the trione I (n = 2; R = Me). Birch[15] has extended the work of Collie and has achieved a biogenetic-type synthesis of dihydropinosylvin (XI) by base treatment of the γ-pyrone (X). In spite of these successes considerable difficulty has been encountered[16] in synthesizing higher members of the linear β-polyketone series and at the beginning of our investigations no general solution to the problem of β-polyketo acid synthesis had emerged.

We therefore elected to extend the pyrone concept as a convenient form of the masked β-polycarbonyl system, and for this we considered several variants which at least seemed open to experimental verification.

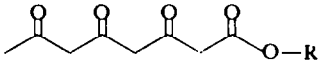


XII

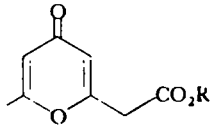
≡



XIII



XIV



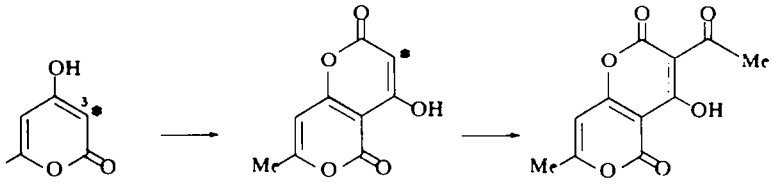
XV

Thus, embodied in the first member of an extended pyrone system (as XII) we find the dehydrated form of the 3,5,7-trioxo-octanoic acid (XIII) bearing a carboxyl group at the 4-position and reminiscent of the kind of intermediate possible in biochemical acetate–malonate condensation with the exception that one of the malonate carboxyl groups has, for the moment, been retained. Decarboxylation of

[13] J. N. Collie and W. S. Meyers, *J. Chem. Soc.* **63**, 122 (1893).
[14] J. N. Collie, *J. Chem. Soc.* **63**, 329 (1893); *Ibid.* **91**, 1806 (1907).
[14a] J. R. Bethel and P. Maitland, *J. Chem. Soc.* 3751 (1962).
[15] A. J. Birch, D. W. Cameron and R. W. Rickards, *J. Chem. Soc.* 4395 (1960).
[16] cf. A. J. Birch, F. Fitton, D. C. C. Smith, D. E. Steere and A. R. Stelfox, *J. Chem. Soc.* 2209 (1963).

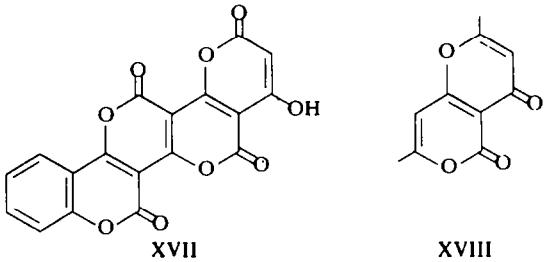
XIII prior to cyclization would lead to 3,5,7-trioxo octanoic acid (XIV; R = OH) whose preparation and cyclization has recently been described.[17]

The results of our experiments with the "condensed" pyrone system (type XII) are now described in detail and later papers will deal with alternative modes of synthesis of polyketide progenitors (e.g. type XV).



XVI XII XIX

Logical extension of the simple tricarbonyl function latent in triacetic acid lactone (XVI) can be made, in principle, by adding further successive units of β-dicarbonyl functionality. Thus we were aware of the condensation of various malonic esters with coumarins[18] to give products such as XVII. Also the synthesis of the pyrono pyrone[19] (XVIII) although not quite belonging to a series relevant for polyketide assembly, still showed that a substantial array of acetyl functions constrained within a polypyrone framework could not only be prepared, but moreover exhibited well-defined physical and chemical properties.†



XVII XVIII

Our first objective was to test the pyrone concept in its simplest form using the new dipyrone XII. The reactivity at the 3-position of triacetic acid lactone (XVI) indicated that such a pyronopyrone could be prepared. In a preliminary experiment cyanoacetic acid[20] and triacetic acid lactone were heated in trifluoroacetic acid solution to give the desired compound XII m.p. 228–230° in 18% yield. The dipyrone XII showed λ_{max} 269 and 328 mμ and displayed CO absorption in the IR spectrum at 1747 and 1705 cm^{-1} due to unbonded (a) and bonded (b) CO function respectively.

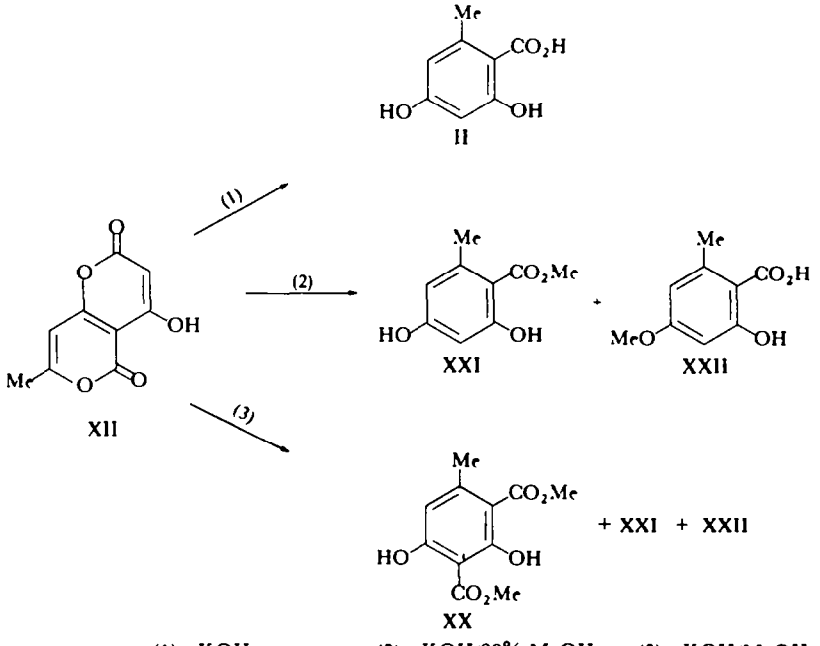
† The conversion of XVIII to a phenolic compound has recently been announced (P. F. Hedgecock, P. F. G. Praill and A. L. Whitear, *Chem. & Ind.* 1268 (1966).

[17] T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.* **88**, 2053 (1966).
[18] F. Ziegler, H. Junch and H. Biemann, *Monatsh.* **92**, 927 (1961).
[19] P. F. G. Praill and A. Whitear, *Proc. Chem. Soc.* 112 (1961).
[20] cf. L. L. Woods and J. Sterling, *Texas J. Science* **15**, 200 (1963).

The very simple NMR spectrum displayed protons at τ 7·44 (Me-singlet), τ 3·30 (H_1 singlet) and τ 4·02 (H_2 singlet).[21] Elemental analysis and mass spectra mol wt determination confirmed the structure. Only a slight improvement in yield (to 21%) was obtained using ethylchloroformyl acetate although the use of excess malonyl chloride[21] in hot trifluoroacetic acid eventually gave a 55–60% yield of XII. The principal by-product of the latter reaction is the acetyl dipyrone (XIX) which could also be prepared by acetylation of XII with acetyl chloride.

The acetyl dipyrone (XIX) was a crystalline compound m.p. 247° with a principal UV max at 347 mμ and protons in the NMR spectrum at τ 7·48 (Me, s), τ 7·1 (Me, s) and τ 3·45 (H_1, s). The formation of the acetyl derivative was welcome testimony to the sustained activity with respect to electrophilic attack at the starred atom in XII. Further elaboration of the condensed pyrone system by another "malonate" unit therefore seemed feasible but before proceeding to this stage, we examined the reactivity of the dipyrone in basic media in order to test our premise at the C_8 level.

Accordingly the dipyrone XII was dissolved in normal aqueous potassium hydroxide solution under nitrogen. Acidification of this solution after 70 min afforded orsellinic acid (6%) as the sole identifiable product. Thus the condensed pyrone XII served

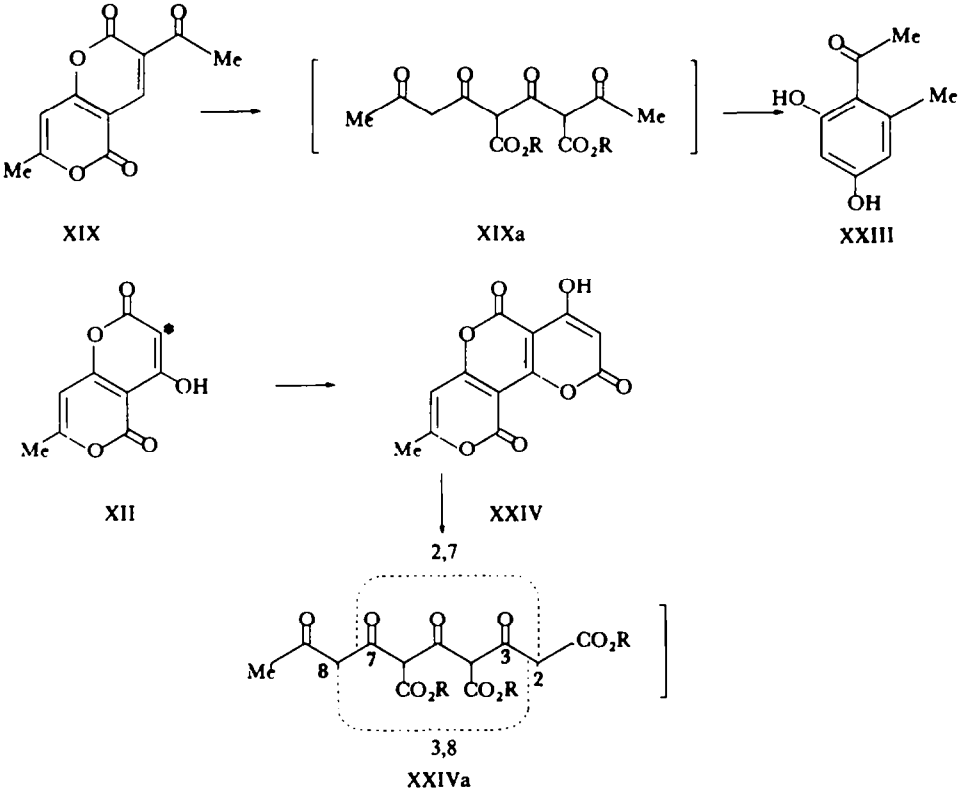


as the progenitor *in vitro* of the naturally-occurring orsellinic acid. In order to assess the effect of other basic media we next examined the effect of *methanolic* potassium hydroxide on XII. In a 35 hr experiment this reagent afforded dimethyl–orcinol dicarboxylate (XX; 5·4%), methyl orsellinate (XXI; 18%) and the monomethyl ether of orsellinic acid which occurs naturally as everninic acid (XXII; 10%). Although

[21] cf. M. A. Butt and J. A. Elvidge, *J. Chem. Soc.* 4483 (1963).

methanolysis of the pyrone at both lactonic termini had occurred, thus retaining all of the carbon atoms of XII in the cyclized product, the mode of closure was unaffected and *aldol condensation* maintained. Finally, when the dipyrone was opened in aqueous methanolic potassium hydroxide solution methyl orsellinate (18%) and the ether (XXII; 5%) were formed. Aqueous alkaline conditions thus promote decarboxylation of the carboxyl group at position 4 of the intermediate triketo acid or ester XIII. A more rigorous test of the synthetic method was now made by passing on to the next homologue, having first subjected the acetyl dipyrone (XIX) to methanolic alkaline conditions to afford orcacetophenone (XXIII) in 6% yield *via* the tetraketone[22] (XIXa).

In principle the same reactivity is retained in the dipyrone with respect to electrophilic attack at the position C* in XII and the condensation of XII with malonyl

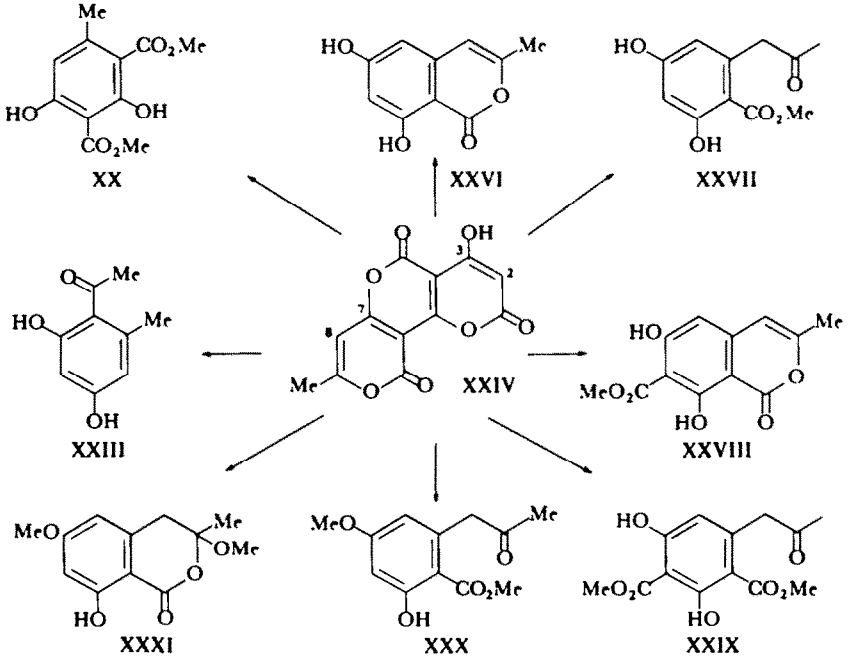


chloride produces the tripyrone XXIV in 20% yield. Preliminary experiments (see Experimental) indicate that a 30% yield of XXIV can be achieved by using bis-(2,4-dichlorophenyl) malonate instead of malonyl chloride. The tripyrone XXIV which is equivalent to one starter acetate combined linearly with four malonate units (XXIVa) is a crystalline high melting compound whose NMR spectrum (Experimental) is almost identical with that of its bicyclic precursor (XII). Two unbonded and one

[22] H. Stettner and S. Vestner, *Chem. Ber.* **97**, 169 (1964).

hydrogen-bonded CO groups appear in the IR spectrum of XXIV and the appropriate shift to longer wavelengths (compared with XII) is found in the UV spectrum. Characterization was completed by mass spectral and analytical data and by the subsequent ring opening reactions which, although complex, clearly show that the pyrone XXIV serves as an excellent model for the production of 3,5,7,9-tetraoxodecanoic acid and its aromatic dehydration products.

Application of the same basic conditions as used above to ring opening of XXIV yielded at first a trivial result. In particular a solution of XXIV in aqueous potassium hydroxide returned the starting material in 50% yield, together with some orcacetophenone (XXIII; 5%), previously obtained from acetyl dipyrone (XIX). The latter compound was indeed formed in small yield by hydrolysis of XXIV with dilute aqueous potassium hydroxide.

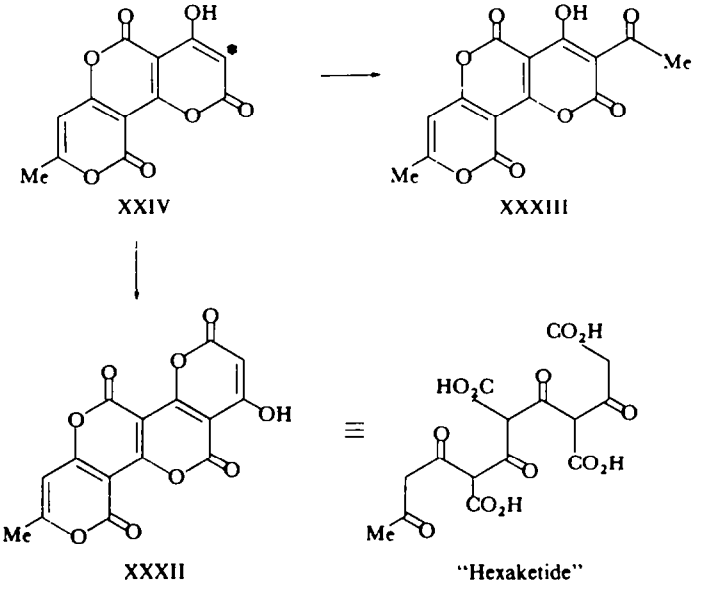


A completely different but welcome result was obtained in methanolic potassium hydroxide solution. After careful chromatography of the crude reaction mixture from this experiment, no fewer than 8 crystalline compounds were obtained in a total of 12–15% yield together with starting material (30%). Six of these compounds are in fact derived by internal aldol condensation of XXIVa at positions 2 and 7. The exceptions are XX and orcacetophenone (XXIII), whose appearance under these conditions is due to prior degradation of XXIV or XXIVa.[23] The remaining products represented conversion of the intact C_{10} chain and are variants of the 2,7-aldol condensation of XXIVa. Perhaps the most significant of these are 6,8-dihydroxy-3-methyl isocoumarin (XXVI)[24] and the methyl ester of C-acetyl orsellinic acid

[23] A. Kamal, M. Ali Khan and A. Ali Qureshi, *Tetrahedron* **19**, 111 (1962).
[24] A. E. Oxford and H. Raistrick, *Biochem. J.* **27**, 634 (1933).

(XXVII) whose identities were confirmed by comparison with authentic samples, the acid XXVII (Me = H) having been previously obtained from Penicillium *brevi-compactum*.[25] The biogenetic simulation of the formation of C_{10} polyketides has thus been achieved. The next products were 7-carbomethoxy-6,8-dihydroxy-3-methyl-isocoumarin (XXVIII) whose structure is based partly on spectroscopic evidence (Experimental) and partly on its conversion to another product of the reaction, *viz.* the dimethyl ester XXIX.

The final two compounds are the methyl ether XXX and the dimethyl derivative of the lactol of C-acetyl orsellinic acid *viz.* 3,4-dihydro-3,6-dimethoxy-8-hydroxy-3-methyl isocoumarin (XXXI).[cf. 24] The close similarity of this biogenetic type synthesis to the construction of naturally-occurring aromatic compounds is thereby nicely illustrated, for while the isocoumarin XXXI may be compared with Raistrick's metabolite,[24] the ether XXX has, since our preliminary communication on this topic, been isolated from *Endothia parasitica*.[26] Clearly several variants of these reaction conditions merit investigation and such studies will be described in later papers of this series. However, since both C_8 and C_{10} aromatic metabolites can be prepared by solution of the polypyrones XII and XXIV respectively in a simple alkaline medium



under mild conditions without recourse to a long search for optimal conditions we felt that it was important at this stage to ensure that the synthetic route to polypyrones could be extended to the precursor of "hexaketide", *viz.* the tetrapyrone XXXII. Once again the design of XXIV is such that if condensation with, for example, bis-(2,4-dichlorophenyl)malonate takes place it will lead to the required compound.

We have found that although the reactivity at C* in XXIV is somewhat impaired (compared with the same reaction on XVI or XII) both acetyl tripyrone (XXXIII)

[25] R. F. Curtis, P. C. Harries and C. H. Hassall, *J. Chem. Soc.* 5382 (1964).
[26] E. Hardegger, W. Rieder, A. Walser and F. Kugler, *Helv. Chem. Acta* **49**, 1283 (1966).

and tetrapyrone (XXXII) can be prepared and once again XXXII exhibits the predicted NMR spectrum identical with that of XXIV.

Since the publication of our initial communication other groups[28,29] have succeeded in converting dipyrones to aromatic compounds. Of particular note is the recent synthesis of β-triketo acids and their conversion, in high yield, to naturally occurring phenolic compounds.[30] A convenient synthesis of β-tetraketones has also been reported.[31]

With the presumed synthetic precursor of C_{12} aromatic compounds in hand, the complexity of ring opening at this level requires some measure of control over subsequent closure reactions of the β-polyketo-acids and -esters. A method for effecting this control has now been established[27] and this, together with further details of polypyrone chemistry will be described in succeeding papers of this series.

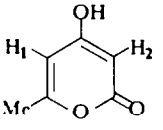
EXPERIMENTAL

UV spectra were measured in EtOH, and IR spectra on KBr discs (unless specified to the contrary). 60 mc NMR spectra were recorded at 20° in trifluoroacetic acid (unless stated otherwise) with TMS as internal standard. Mass spectra were obtained on an A.E.I. MS 9 instrument at 70 ev. with a direct insertion probe.

Preparation of polypyrones

Dehydroacetic acid IX (Eastman Organic Chemicals) was deacetylated to *triacetic acid lactone* (XVI) by the method of Butt and Elvidge.[21] The latter had m.p. 190–191° (dec) λ_{max} 284 mμ (ε 6750) ν_{max} (Nujol) 1720, 1660, 1630, 1590 cm^{-1}

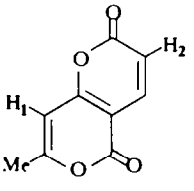
NMR



τ	
3·48, m	(H_1)
3·79, d	(H_2; J H_1, H_2 = 2 c/s)
7·53, s	($C\underline{H}_3$)

The dipyrone (XII). (a) To a soln of triacetic acid lactone (100 g) in trifuloroacetic acid (300 ml) was added malonyl chloride (222 g). The resultant deep red-brown soln was maintained at reflux temp with exclusion of moisture for 5 hr. After cooling to 0° AcOEt (130 ml) was added and after 10 min the crude ppt (100 g) collected by filtration. Filtration of a Chf soln (13 l) through a silica gel column (400 g, 35 × 5 cm) removal of solvent and recrystallization from Chf gave pure XII (82 g; 53%) m.p. 230–232°, λ_{max} 271 and 392 mμ (ε 11,800 and 7300); λ_{min} 234 and 292 mμ (ε 1500 and 2700); ν_{max} (Nujol) 3200, 3050, 1755, 1690, 1625, 1560 cm^{-1}.

NMR



τ	
3·30, s	($\underline{H}_1$)
4·02, s	($\underline{H}_2$)
7·44, s	($C\underline{H}_3$)

[27] T. Money, J. Douglas and A. I. Scott, *J. Am. Chem. Soc.* **88**, 624 (1966).
[28] L. Crombie and A. W. G. James, *Chem. Comm.* 357 (1966).
[29] P. F. Hedgecock, P. F. G. Praill and A. L. Whitear, *Chem. & Ind.* 268 (1966).
[30] T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.* **88**, 2053 (1966).
[31] G. Casnati, A. Quilico, A. Ricca and P. Vita Finzi, *Tetrahedron Letters* 233 (1966).

(Found: C, 55·90; H, 3·19; O, 41·28%; M = 194. $C_9H_6O_5$ requires: C, 55·68; H, 3·12; O, 41·21%; M = 194.)

Later washings of the column afforded XIX (5%) m.p. 245–247° identical with a sample prepared as described below.

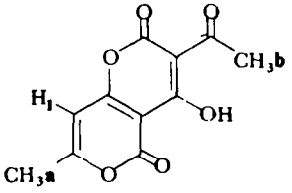
(b). Triacetic lactone (10·06 g) and cyanoacetic acid (12·11 g) were dissolved in trifluoroacetic acid (30 ml) and refluxed under N_2 for 6 hr. Water (10 ml) was added and the orange reaction soln heated to boiling for 5 min, and allowed to cool. Treatment with AcOEt (40 ml) and cooling to 0° yielded XII (2·81 g, 18%) m.p. 225–230°.

(c) Ethyl chloroformyl acetate (1·02 g) was added over a 30 min period to a soln of triacetic lactone (646 mg) in trifluoroacetic acid (1 ml) held at 112° in an oil bath for 3 hr. HCl was evolved. The reaction mixture was heated to reflux to destroy excess acid chloride, and allowed to cool to room temp. Crystallization from Chf gave XII (206 mg, 21%) m.p. 228–230°. Comparison by TLC with the product from the reaction (a) showed the product from the two sources to be identical.

Acetyl dipyrone (XIX). The pyrone XII (1·9 g) was dissolved in trifluoroacetic acid (4 ml), AcCl (2·2 ml) added and the mixture heated on the steam bath for 2 hr. Addition of ice water, filtration and crystallization from Chf gave prisms (1·2 g; 52%) m.p. 245–252°.

Filtration in chloroform soln through silica gel gave colourless needles (from $CHCl_3$) m.p. 245–247°. λ_{max} 225, 261, 347 mμ (ε 12,800, 6400, 1400); ν_{max} 1765, 1730, 1638, 1550 cm^{-1}.

NMR

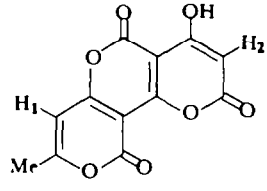


7·48, s (C$\underline{H}_3$a)
7·10, s (C$\underline{H}_3$b)
3·45, s (H_1)

(Found: C, 55·76; H, 3·50; O, 40·74%; M = 236. $C_{11}H_8O_6$ requires: C, 55·95; H, 3·41; O, 40·64%; M = 236.)

Tripyrone (XXIV). To a soln of XII (10 g) in trifluoroacetic acid (20 ml) was added malonyl chloride (59 g) and the reaction held at 100° for 1½ hr. The cooled mixture was triturated with ether (50 ml) and the resultant crude product chromatographed on silica gel. Elution with chloroform afforded first bispyrone (2 g) then the trispyrone (2·7 g; 20%) as yellow needles after recrystallization from acetone m.p. 260° (dec). λ_{max} 281, 360, 370 mμ (ε 8700, 8900, 8900); ν_{max} (Nujol) 3200, 1755, 1720, 1635 cm^{-1}.

NMR



τ
3·30, m (H_1)
3·96, s (H_2)
7·43, s (C$\underline{H}_3$)

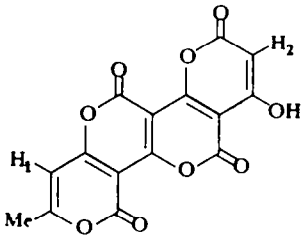
(Found: C, 54·95; H, 2·59; M = 262. $C_{12}H_6O_7$ requires: C, 54·97; H, 2·31%; M = 262.)

Acetyltripyrone (XXXIII). To tripyrone (517 mg) dissolved in trifluoroacetic acid (3 ml) was added AcCl (1·9 ml). The mixture was heated on a steam bath for 24 hr then the reaction mixture was poured into ice water (25 ml) precipitating a yellow sold which was filtered off and washed several times with cold water. The crude material was dissolved in hot AcOEt (600 ml), treated with activated charcoal, and filtered. The pale yellow filtrate was concentrated *in vacuo* until crystallization occurred with cold AcOEt, yield: 410 mg, 68%, m.p. 285–290° (dec). λ_{max} 430 mμ (ε 2000) shoulder, 390 mμ (ε 12,000) shoulder, 373 mμ (ε 16,000) 269 mμ (ε 9000); ν_{max} (Nujol) 1750, 1640, 1600, 1540 cm^{-1}. NMR 7·45 τ (3H), 7·18 τ (3H), 3·40 τ (1H).

(Found: C, 55·02; H, 2·50; O, 42·48. $C_{14}H_8O_6$ requires: C, 55·27; H, 2·65; O, 42·08%.)

Tetrapyrone (XXXIV). Tripyrone XXIV (300 mg) and bis-(2,4-dichlorophenyl) malonate (550 mg) were heated at 250–255° for 2 min. The product was dissolved in benzene and chromatographed on silica gel. Elution with chloroform gave (in the later fractions) almost pure XXXIV (120 mg, 31%) finally purified by sublimation at 195°/0·01 mm and recrystallization from acetone to give tiny orange prisms, m.p. 280° (dec). λ_{max} 272, 385, 398, 420 mμ (ε 8600, 9800, 9800, 6000; λ_{min} 243, 318 mμ (ε 5800, 3800); ν_{max} 1755, 1705, 1645, 1590 cm^{-1}.

NMR



τ

3·43, s (H_1)
3·99, s (H_2)
3·45, s ($C\underline{H}_3$)

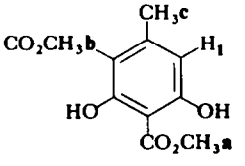
(Found: C, 54·67; H, 2·02; M = 330. $C_{15}H_6O_9$ requires: C, 54·56; H, 1·83%; M = 330·2.)

Polyketide Generation and Cyclization

1 *Dipyrone* XII

(a) *With aqueous alkali.* Dipyrone XII (2·2 g) was dissolved in 1N KOH (150 ml), kept under N_2 at room temp for 70 min, then acidified to pH 2 at 0° with conc HCl. The freeze dried concentrate of this preparation was extracted with acetone and the soln concentrated to leave, after removal of some AcOK crystalline orsellinic acid (123 mg, 6%) identical with an authentic sample (TLC, m.p. mixed m.p., IR spectra).

(b) *With methanolic potassium hydroxide.* A soln of XII (3·0 g) in methanolic 1N KOH (1200 ml) was kept under N_2 for 35 hr. Removal of solvent *in vacuo* to 250 ml, addition of ice–water (250 ml) and adjusting the pH to 6 at 0° precipitated feathery needles of XX (200 mg; 5·4%) m.p. 112–113°; $\lambda\lambda_{max}$ 232, 247, 260 sh, 315 mμ (ε 33,000, 5600, 12,400, 5600); $\lambda\lambda^{OH^-}_{max}$ 289 (ε 10,000); ν_{max} 1650, 1620, 1570 cm^{-1}.



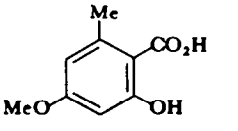
τ

3·48 (H_1)
5·85 ($C\underline{H}_3$a)
5·91 ($C\underline{H}_3$b)
7·53 ($C\underline{H}_3$c)

(Found: C, 55·27; H, 5·24; O, 39·5; M = 240. $C_{11}H_{12}O_6$ requires: C, 55·00; H, 5·05; O, 39·95%; M = 240.) The filtrate was extracted with Chf and the extract evaporated to give XXI (0·5 g; 18%) m.p. 138–140° identical with an authentic sample. NMR (deuteroacetone) τ −1·58 (OH bonded), τ 1·03 (aromatic OH), τ 3·73 (2H; aromatic), τ 6·11 ($OC\underline{H}_3$), τ 7·54 ($-C\underline{H}_3$).

The aqueous layer from the Chf extraction was acidified (to pH 2) and extracted with Chf as before to afford XXII (220 mg; 3%) m.p. 166° (depends on rate of heating) lit. m.p. 160–170°—depending on rate of heating). $\lambda\lambda_{max}$ 260, 302 mμ (ε 7410, 2621); ν_{max} 1640, 1585 cm^{-1}.

NMR



τ

3·64 (2H; aromatic)
6·16 ($OC\underline{H}_3$)
7·43 ($C\underline{H}_3$)

(c) *With aqueous methanolic potassium hydroxide.* Dipyrone (1·47 g) was dissolved in methanolic 1N KOH (10% aqueous; 150 ml) and kept under nitrogen for 48 hr. Working up as in (b) yielded XXII (65 mg; 4·7%) m.p. 166° and methyl orsellinate (251 mg; 18%).

II *Acetyldipyrone* (XIX)

A soln of XIX (1·42 g) in methanolic 1N KOH (3000 ml) was worked up as in I(b) after 48 hr to yield XXIII (65 mg; 6%) m.p. and mixed m.p. 158°; $\lambda\lambda_{max}$ 233, 283 mμ (ε 5960, 7560); ν_{max} 1610, 1565 cm^{-1} NMR τ −3·99 (O<u>H</u>), τ −0·13 (O<u>H</u>), τ 3·73 (2H; aromatic), τ 7·40 (—COC<u>H</u>$_3$), τ 7·48 (—C<u>H</u>$_3$).

III *Tripyrone* (XXIV)

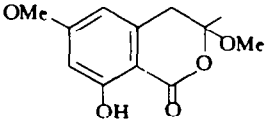
(a) *With aqueous alkali.* A soln of XXIV (200 mg) in 1N KOH (120 ml) was kept under N_2 for 90 min. The initial dark green colour changed to orange within 5 min. Working up as in I(a) afforded a crude product (140 mg) which was shown by TLC to be largely unchanged XXIV. Preparative TLC on silica using $CHCl_3$: HOAc (9:1) as solvent afforded orcacetophenone (30 mg) and mixed m.p. and m.p. 157–158° as well as XXIV (100 mg).

(b) *With methanolic potassium hydroxide solution.* A mixture of XXIV (1 g) and methanolic 1N KOH (1 l) was stirred under N_2 for 48 hr. After 24 hr complete soln had occurred. The soln was acidified with conc HCl (80 ml), concentrated *in vacuo* to 130 ml and water (200 ml) added. Chloroform extraction gave a "$CHCl_3$ extract" (600 mg) whilst freeze drying of the aqueous layer and acetone extraction afforded an "aqueous extract" (300 mg). Two further runs of the experiment were made to give finally "$CHCl_3$ extract" (2·0 g) and "aqueous extract" (1·0 g). The "aqueous extract" was shown by TLC and IR evidence to consist largely of trispyrone. In addition an aromatic component was isolated by preparative TLC and was shown to be *orcacetophenone* XXIII (95 mg) by comparison with an authentic sample. The $CHCl_3$ extract was separately purified by preparative TLC on 20 × 60 × 0·10 cm plates spread with silica gel using benzene:ether (4:1) [system 1] or CCl_4; $CHCl_3$; HOAc (10:9:1) [system 2] as developing solvent mixtures. Detection of bands was made using a fluorescent indicator (G.E. Electronic Phosphor) and the bands eluted with chloroform–acetone mixtures. In order of their R_f in system 1 these were:

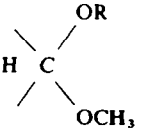
(1) *Dimethylorcinol 2,4-dicarboxylate* XX (12 mg). R_f 0·60 m.p. 108–110° identical with the sample prepared as above.

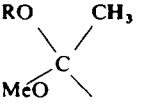
(2) 3,4-*Dihydro*-3,6-*dimethoxy*-8-*hydroxy*-3-*methyl isocoumarin* XXXI. (23 mg) R_f 0·55 m.p. 101° from hexane, λ_{max} 216, 268, and 303 mμ (ε 21,400, 13,300, and 5,600); ν_{max} 1675, 1640, 1540 cm^{-1}.

NMR (deuteroacetone)



τ

1·28, s O<u>H</u> (phenolic)
3·65, s 2H (aromatic)
6·17, s 3H (Ar-OC<u>H</u>$_3$)
6·68, s


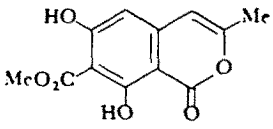
6·84, s 2H (benzylic)


8·37, s 3H

(Found: C, 60·49; H, 6·12; M = 238. $C_{12}H_{14}O_5$ requires: C, 60·50; H, 5·92%; M = 238.) $FeCl_3$: dark red.

(3) 7-*Carbomethoxy*-6,8-*dihydroxy*-3-*methylisocoumarin* XXVIII. (95 mg) R_f 0·50 m.p. 196–198° (from EtOAc). λ_{max} 257, 291, 303, 340 mμ (ε 39,000, 8400, 8300, 7700); ν_{max} 1685, 1650, 1625, 1570 cm^{-1}.

NMR ($CDCl_3$)

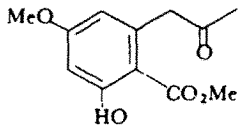


τ		
−2·78	1H	Phenolic OH
−2·42	1H	
3·72	1H	Ar-H
3·86	1H	olefinic H
6·00	3H	OCH_3
7·75	3H	CH_3—C=C

(Found: C, 57·73; H, 4·51; M = 250. $C_{12}H_{10}O_6$ requires: C, 57·60; H, 4·03%; M = 250.) Gibbs Test: Positive.

(4) (*2-Carbomethoxy-3-hydroxy-5-methoxyphenyl)propan-2-one* XXX. (4 mg) R_f 0·45 m.p. 101–103° (benzene–hexane). λ_{max} 258 and 310–320 mμ (ε 11,300 and 2800); ν_{max} 3400, 1710, 1660, 1620 1585 cm^{-1}.

NMR ($CDCl_3$)

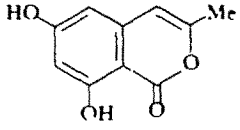


τ		
−1·51	1H	phenolic OH
3·41	1H	Ar-H
3·72	1H	
6·06	3H	OCH_3
6·15	3H	OCH_3
6·37	2H	Benzylic H_2
7·82	3H	CH_3—CO—

Mass spectrum: Parent 238, 206, 164 (base peak). $C_{12}H_{14}O_5$ requires: M = 238.

(5) *6,8-Dihydroxy-3-methylisocoumarin* XXVI†. (40 mg) R_f 0·40 m.p. 250–253° (from aqueous acetone) (lit. m.p. 245–248°, 244–248°). λ_{max} 237, 245, 278, 289, and 324 mμ (ε 42,000, 49,000, 7000, 5200, 6200); ν_{max} 3250, 1685, 1625, 1580 cm^{-1}.

NMR (deuteroacetone)



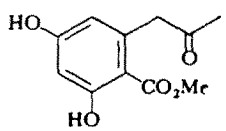
τ		
−1·17	1H	Phenolic bonded
0·47	2H	Phenolic non-bonded
3·62	3H	ArH(2) and olefinic H superimposed
7·78	3H	CH_3—C C

(Found: C, 61·90; H, 4·41; M = 192. Calc for $C_{10}H_8O_4$: C, 62·5; H, 4·20%; M = 192.)

The compound was identical with the dehydration product of C-acetyl orsellinic acid (m.p., mixed m.p., IR spectra).

(6) *C-Acetyl methyl orsellinate* XXVII. (30 mg) R_f 0·20 m.p. 130° (from AcOEt–hexane). λ_{max} 215, 265, 303 mμ (ε 20,000, 11,900, 5520); ν_{max} 3410, 1700, 1670, 1625, 1610 cm^{-1}.

NMR (deuteroacetone)



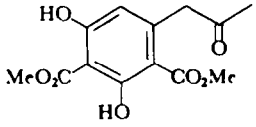
τ		
−1·51	1H	Phenolic bonded
0·5	1H	Phenolic unbonded
3·66, d	1H	meta coupled
3·73, d	1H	J = 2·4 c/s
6·00	2H	$ArCH_2CO$
6·05	3H	OCH_3
7·83	3H	CH_3—CO

† We thank Dr. I. H. Qureshi for his able help with this experiment.

(Found: C, 58·97; H, 5·48; M = 224. $C_{11}H_{12}O_5$ requires: C, 58·92; H, 5·40%; M = 224.)

(7) 2,4-*Dicarbomethoxy*-3,5-*dihydroxyphenylpropan*-2-*one* XXIX. (20 mg) R_f 0·40 (system 2) m.p. 149–151° (benzene–hexane). λ_{max} 231, 148, 316 mμ (ε 14,600, 11,800, 3500); ν_{max} 1710, 1665, 1610, 1570 cm^{-1}.

NMR ($CDCl_3$)



−2·62	1H } Phenolic OH
−1·781	1H }
3·64	1H Ar-H
5·97	3H OCH_3
6·11 (br)	5H $—CH_2—$
7·84	3H CH_3CO

Mass spectrum *m/e* 284 (parent) 252, 219, 209 (base peak) 176. Gibbs Test: Positive.

Conversion of XXVIII *to* XXIX. A soln of XXVIII (5 mg) in 0·2M NaOH (2 ml) was heated at 120° for 20 min. Cooling, acidification and ether extraction afforded acidic material which was esterified with diazomethane to give a product m.p. and mixed m.p. 145–150° with IR, UV, and TLC characteristics identical with those of XXIX.

We acknowledge with thanks the provision of samples of orsellinic acid (by Dr. R. Thomas), 6,8-dihydroxy-3-methylisocoumarin (by Professor C. H. Hassall), and diaporthinic acid methyl ester (by Professor E. Hardegger).

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