Tetrahedron. Vol. 23, pp. 3545 to 3555. Pergamon Press Ltd. 1967. Printed in Great Britain

PYRONE STUDIES—II*

BIOGENETIC-TYPE SYNTHESIS OF PHENOLIC COMPOUNDS

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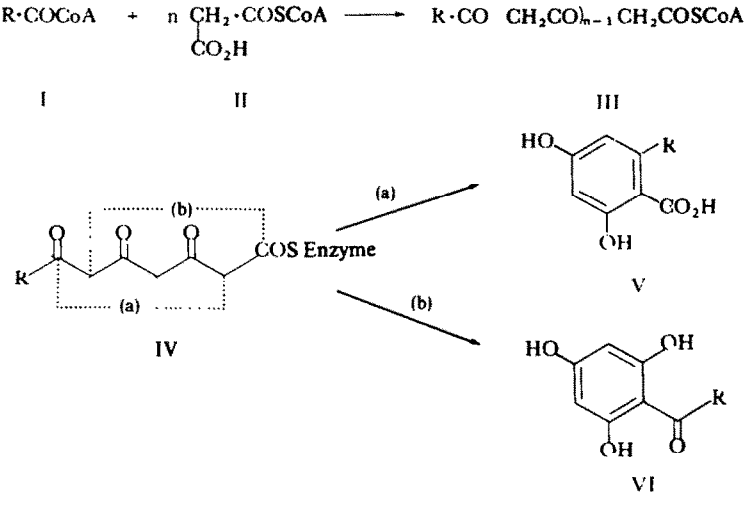
(*Received* 23 *December* 1966; *accepted for publication* 11 *January* 1967)

Abstract—Further studies on the use of pyrones for the biogenetic-type synthesis of phenolic compounds are reported. In particular some control over the direction of cyclization of the intermediate β-triketo ester chain is demonstrated. This control makes possible the synthesis of two basic types of phenolic compound from the same precursor and is analogous to the probable biosynthesis of these compounds in the natural system.

ACCORDING to the polyacetate hypothesis[1-3], a large proportion of naturally occurring phenolic compounds (polyketides) may be derived by intramolecular condensation of a linear β-polyketo acid derivative (III). Structural analysis and tracer studies[2,4,5] indicate that the activated forms of acetic, propionic and cinnamic



* Preliminary Communication, *J. Am. Chem. Soc.* **88**, 624 (1966), Part I: *J. Am. Chem. Soc.* **87**, 3004 (1965); *Tetrahedron* **23**, 2535 (1967).

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

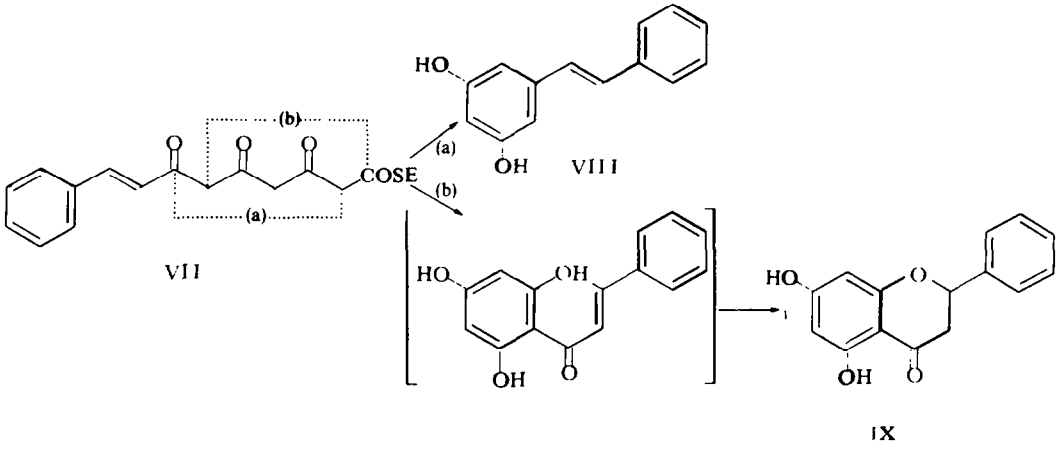
[2] A. J. Birch and F. W. Donovan, *Austral. J. Chem.* **6**, 360 (1953); A. J. Birch, *Proc. Chem. Soc.* 3 (1962).

[3] R. Robinson, *Structural Relations of Natural Products*, Clarendon Press, Oxford, 1955.

[4] J. H. Richards and J. B. Hendrickson, *The Biosynthesis of Steroids, Terpenes and Acetogenins*, Benjamin, New York (1964).

[5] J. D. Bu'Lock, *The Biosynthesis of Natural Products*, McGraw-Hill, London (1965).

acid commonly function as chain-initiating units (I) while the chain-building unit is presumably malonyl coenzyme A (II). Many phenolic compounds can be formally derived from a β-triketo acid intermediate (IV) and two alternative condensation modes provide a satisfactory explanation for the formation of these compounds. Aldol condensation (IVa) produces substituted orcinols (V) while internal Claisen condensation (IVb) yields acylphloroglucinols (VI). It is also considered possible that the two modes of cyclization can occur in the same biological system and the co-occurrence of flavonoids and stilbenes in many pine heartwoods[6] tends to substantiate this proposal.[2] For these two groups of natural products the same biosynthetic intermediate (VII) can be postulated and the formation of pinocembrin (IX) and pinosylvin (VIII) (which often co-occur)[6] can be rationalized in terms of the condensation modes described above. Support for these biosynthetic routes has been obtained from tracer studies.[4,5] These have shown that cinnamic and acetic acids are incorporated into flavonoids, isoflavonoids and stilbenes in the specific manner required by theory.[2] More recent studies[22,23] have demonstrated the importance of flavanones[28,29] as precursors of the flavonoids and isoflavonoids.

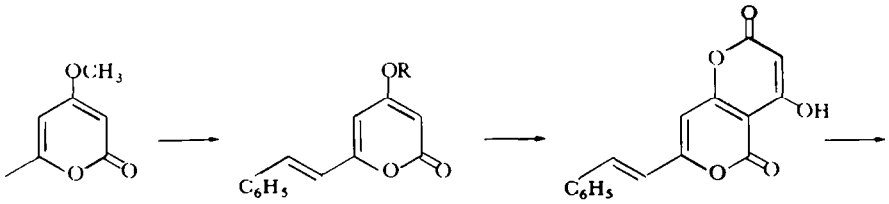


This paper describes our attempts to simulate the biosynthetic route to flavanones and stilbenes. Our previous studies[7-9] have shown the value of using condensed pyrone structures in the construction of synthetically inaccessible β-polyketo acid chains and have demonstrated that compounds of this type can be smoothly converted to phenolic compounds of predictable structure.

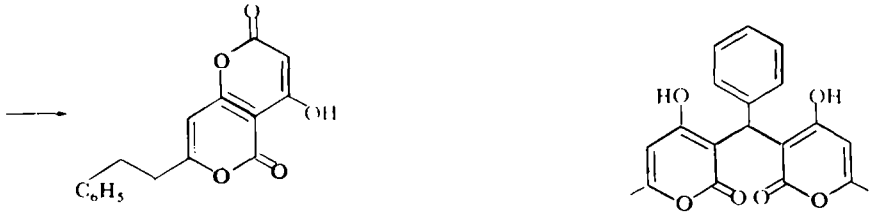
The results reported here provide further evidence for the general applicability of this approach and moreover indicate that the type of condensation which occurs can be predicted by a suitable choice of reaction conditions. The compounds used in this study were the styryl dipyrone (XII) and its dihydro derivative (XIII). The former compound may be considered potentially equivalent (see XII, bold lines) to the β-triketo acid precursor (VII) postulated by Birch to explain the biosynthesis of the flavonoids and stilbenes. The synthesis of the pyrones (XII) and (XIII) followed

[6] G. Linstedt and A. Misiorny, *Acta Chem. Scand.* **5**, 121 (1951).
[7] T. Money, I. H. Qureshi, G. R. B. Webster and A. I. Scott, *J. Am. Chem. Soc.* **87**, 3004 (1965).
[8] T. Money, J. L. Douglas and A. I. Scott, *J. Am. Chem. Soc.* **88**, 624 (1966).
[9] T. Money, F. W. Comer, G. R. B. Webster, I. G. Wright and A. I. Scott, *Tetrahedron* **23**, 2535 (1967).

reasonably well-established routes. Thus condensation of triacetic acid lactone methyl ether (X) with benzaldehyde in the presence of magnesium methoxide[10] yielded the styryl monopyrone methyl ether (XI; R = CH_3)[11,13] which, on treatment with hydrobromic acid,[14] was smoothly converted to the desmethyl compound (XI; R = H)[12,13]



X XI XII



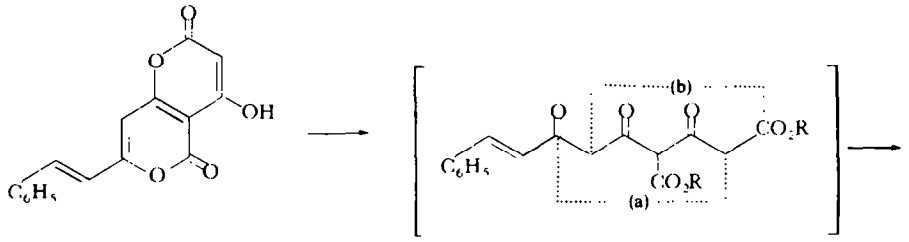
XIII XIV

It may be noted that our attempts to synthesize (XI; R = H) by the method of Vulson *et al.*[15] failed. The synthesis was carried out as described by condensing benzaldehyde with triacetic acid lactone in the presence of piperidine and acetic acid. However the only product isolated was the compound (XIV) (λ_{max} 290, ε 13,300) which was characterized on the basis of analytical and spectral evidence. An identical compound has previously been reported by Borsche[16] and was obtained by condensation of triacetic acid lactone with benzaldehyde under basic conditions. Our successful synthesis (based on the work of Bu'Lock and Smith[10]) gave (XI; R = H), possessing almost identical spectral characteristics (λ_{max} 348, ε 20,000) with those previously reported by Chmielewska.[13] By contrast, the absorption maximum (288 mμ) reported by Vulson *et al.*[15] is in the region associated with simple 4-hydroxy-2-pyrones (cf. triacetic acid lactone λ_{max} 284, ε 7800).

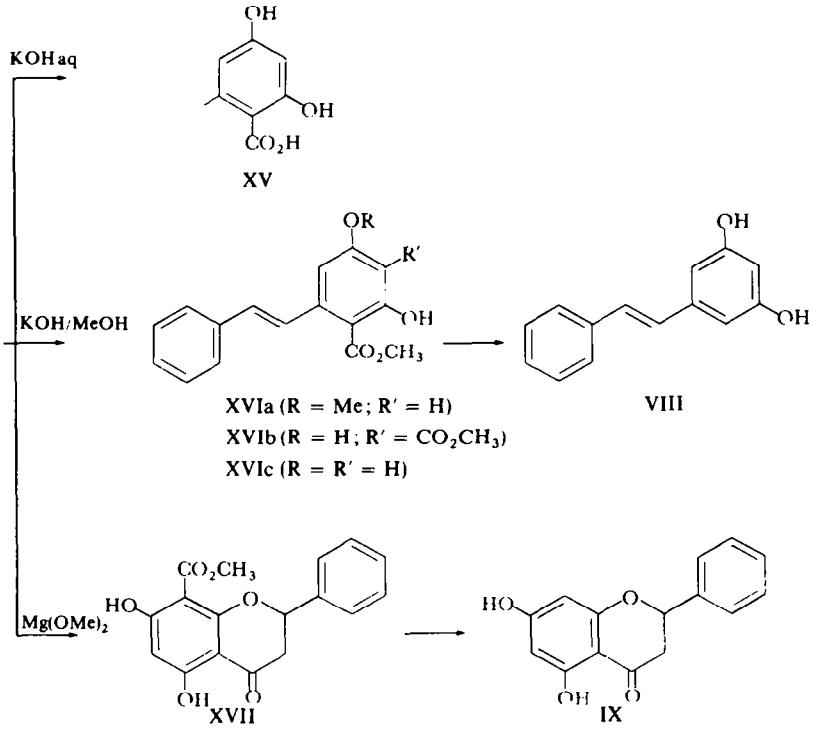
The styryl dipyrone (XII) was obtained by reaction of (XI; R = H) with malonyl dichloride in refluxing trifluoroacetic acid.[17] Catalytic hydrogenation of (XII) yielded the dihydro derivative (XIII). Several sets of basic conditions were used to produce ring opening and subsequent intramolecular condensation. Initial experiments

[10] J. D. Bu'Lock and H. G. Smith. *J. Chem. Soc.* 502 (1960).
[11] F. M. Dean, *Naturally Occurring Oxygen Ring Compounds* p. 83, Butterworths, London (1963).
[12] Z. Macierewicz, *Roczn. Chem.* **24**, 144 (1950).
[13] I. Chmielewska, J. Cieslak, K. Gorczynska, B. Kontnik and K. Pitakowska, *Tetrahedron*, **4**, 36 (1958).
[14] cf. C. H. Stetter and C. Schellhammer, *Liebigs Ann.* **605**, 58 (1957).
[15] N. S. Vulson, E. V. Sarenkova and L. B. Senyarina, *Zh. Obshch. Khim.* **34**, 2743 (1964).
[16] W. Borsche and B. K. Blount. *Chem. Ber.* **65B**, 820 (1932).
[17] cf. M. Butt and J. Elvidge, *J Chem. Soc.* 4483 (1963).

indicated that mild heating with aqueous potassium hydroxide resulted in the formation of orsellinic acid (XV). However, the dealdolisation reaction which produced this compound was not encountered when methanolic potassium hydroxide was used. Under these conditions stilbene derivatives (XVIa–c) were obtained, presumably via aldol condensation of the β-polyketo intermediate (process a). The production of methyl esters under these conditions is unexceptional since the methoxide anion is the predominant basic species in methanolic potassium hydroxide.[18]



XII XIIa



XV

XVIa (R = Me; R′ = H)
XVIb (R = H; R′ = CO_2CH_3)
XVIc (R = R′ = H)

VIII

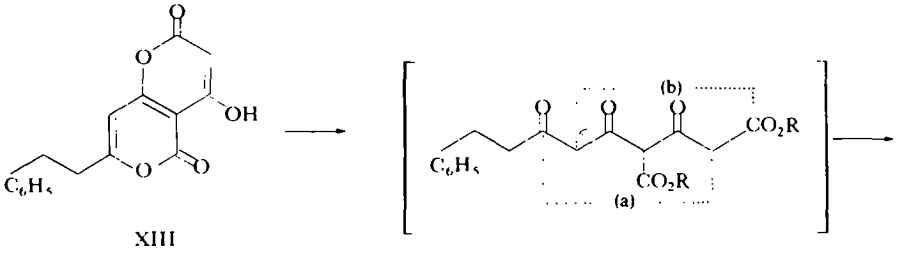
XVII IX

The structures assigned to these compounds are in agreement with spectroscopic and analytical evidence (see Experimental). Further confirmation was obtained by

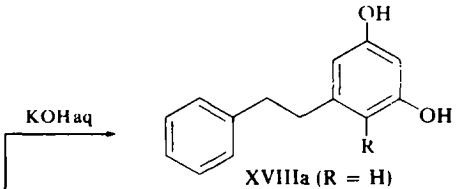
[18] E. F. Caldin and G. Long, *Nature, Lond.* **172**, 583 (1953).

chemical transformation to the natural stilbene, pinosylvin (VIII).* In the case of (XVIa) this was achieved by treatment with hydrobromic acid/acetic acid while methanolic sodium hydroxide effected a similar conversion of (XVIb) and (XVIc). Since the publication of our preliminary communication[8] an elegant synthesis of pinosylvin from a β-triketo precursor (cf. VII) has been reported.[27]

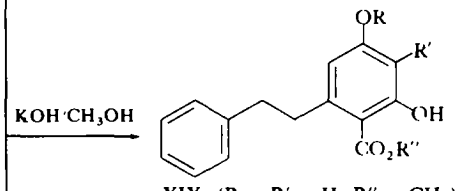
By contrast, treatment of the dipyrone (XII) with methanolic magnesium methoxide[19] produced the flavanone (XVII). Spectroscopic and analytical evidence were



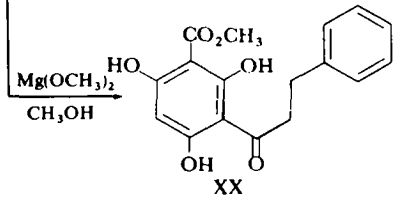
XIII



XVIIIa (R = H)
XVIIIb (R = CO_2H)



XIXa (R = R' = H; R'' = CH_3)
XIXb (R = CH_3; R' = R'' = H)
XIXc (R = H; R' = CO_2CH_3; R'' = CH_3)

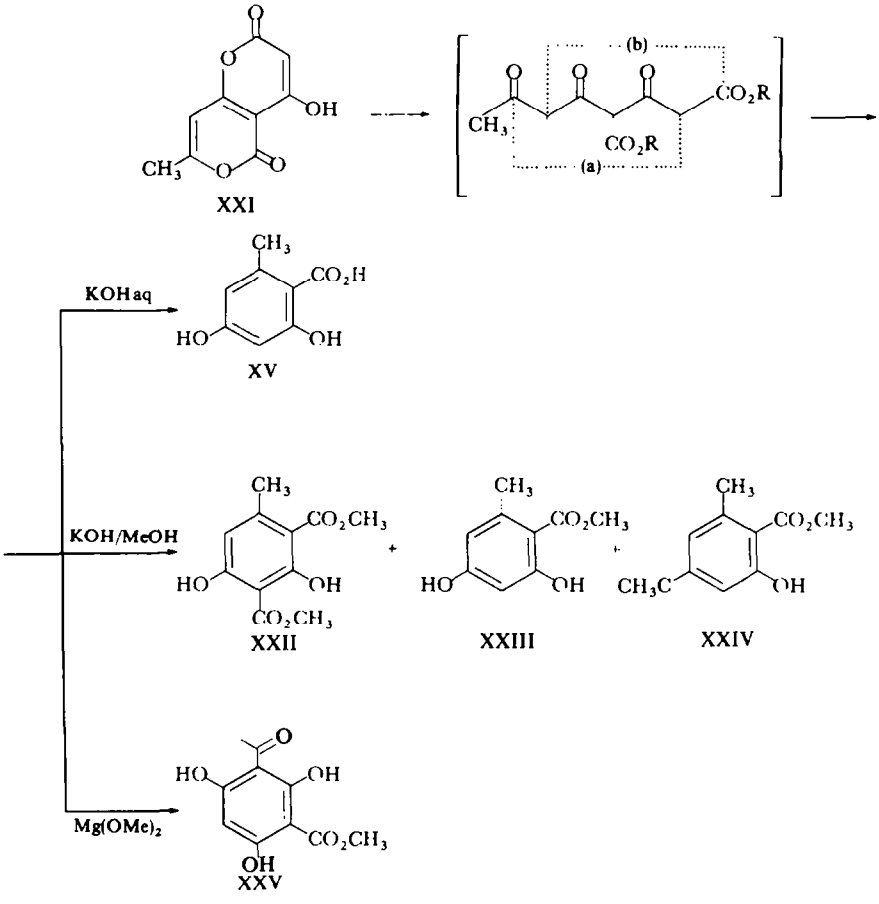


XX

* A sample of authentic pinosylvin was kindly supplied by Dr. Eric Swan, Forest Products Laboratory, Department of Forestry of Canada, Vancouver 8, Canada.

[19] cf. L. Crombie, D. E. James and M. H. Knight, *Tetrahedron Letters*, No. 33, 2313 (1964).

in agreement with this structure except that the position of the carbomethoxy group could not be unambiguously assigned. However on the basis of a negative Gibbs test the 8-carbo-methoxy alternative (XVII) was chosen. Further structural evidence was obtained by conversion of (XVII) under alkaline conditions to a product whose spectroscopic properties were identical to those of authentic pinocembrin (IX).* The production of (XVII) represents a Claisen condensation of the β-tricarbonyl intermediate (XIIa; b) to yield a chalcone intermediate which can then cyclize in the expected manner. The co-occurrence of pinosylvin (VIII) and pinocembrin (IX) has been noted and the reactions described above constitute a biogenetic-type synthesis of flavanones and stilbenes from the same precursor.



The satisfactory nature of these results was duplicated with the dihydro derivative (XIII). Thus treatment with methanolic potassium hydroxide yielded the dihydrostilbenes (XIXa-c) while aqueous potassium hydroxide produced the related compounds (XVIIIa, b). It should be noted (see experimental) that the assignments (XIXa) and (XVIIIa) are tentative. The formation of these compounds demonstrates the preference for aldol condensation of the β-polyketo ester chain under these conditions.

* A sample of authentic pinocembrin was kindly supplied by Professor H. Erdtman, Royal Institute of Technology, Stockholm.

By contrast, and in keeping with our previous findings, magnesium methoxide treatment of (XIII) initiated Claisen condensation with the expected formation of the dihydrochalcone (XX).

That the choice of basic conditions employed determines the mode of ring closure was further demonstrated with the dipyrone (XXI).[7-9] Thus while aqueous potassium hydroxide produced orsellinic acid (XV) and methanolic potassium hydroxide produced methyl orsellinate (XXIII), methyl everninate (XXIV) and the di-ester (XXII), treatment of (XXI) with methanolic magnesium methoxide yielded the acyl-phloroglucinol (XXV).

The control which has been exercised over the direction of condensation of the intermediate β-triketo esters is parallel to the unknown but presumably enzymic control exhibited in natural systems. The role of magnesium methoxide is specific in the examples described here,* and is probably due to prior chelate formation. Since the publication of our preliminary communication Crombie *et al.*[24] have commented on the possibility of chelate formation in more detail. We are presently investigating the role of magnesium ions in these reactions.

Variations of the theme expressed above are being actively investigated and will be the subject of forthcoming communications.

EXPERIMENTAL

Unless otherwise indicated the following experimental conditions are implied. IR spectra were obtained as Nujol mulls with a Perkin-Elmer Model 137B spectrometer and UV spectra in 95% ethanol with a Cary Model 11 or 14. The NMR spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as internal standard (values in τ units) and the mass spectra with an Atlas-CH 4 spectrometer. Melting points were determined on a Kofler heating stage and are uncorrected. Thin layer chromatographic (TLC) results were obtained using glass plates spread with silica gel G (Merck) 0·25 mm thick (0·5 mm for preparative plates). Developed plates were visualized with iodine vapour. Solvent A is chloroform:acetic acid (90:10); Solvent B is carbon tetrachloride:chloroform:acetic acid (50:45:5).

Triacetic acid lactone[17,20,21]

Commercial dehydroacetic acid (100 g) was dissolved in 90% sulfuric acid (165 ml) and heated under nitrogen in an oil bath until the temperature of the solution had reached 130°. The temperature was maintained at 130–136° for 5 min and then the solution was cooled and added to ice-water (700 ml). Crystallization was essentially complete within 5 min and the solid product collected and recrystallized from ethyl acetate (48·6 g; 65%) m.p. 190–191°: lit.[21] m.p. 188–189°.

Triacetic lactone methyl ether (X)

This was prepared by the method of Bu'Lock and Smith.[10]

* More recent studies[25] indicate that other pyrone substrates behave in a similar manner.

[20] D. J. Cram and F. W. Cranz, *J. Am. Chem. Soc.* **72**, 595 (1950).
[21] J. N. Collie, *J. Chem. Soc.* **59**, 607 (1891).
[22] L. Patschke, W. Barz and H. Grisebach, *Z. Naturforsch.* **21**, (3) 201 (1966).
[23] E. Wong and E. Moustafa, *Tetrahedron Letters* 3021 (1966).
[24] L. Crombie and A. W. G. James, *Chem. Comm.* 357 (1966).
[25] J. Douglas and T. Money, unpublished observations.
[26] H. Erdtman, *Progr. Org. Chem.* **1**, 22 (1952).
[27] T. M. Harris and R. L. Carney, *J. Am. Chem. Soc.* **88**, 2053 (1966).
[28] A. J. Birch, *Biogenesi delle Sostanze Naturali*, p. 57. Academia Nationale dei Lincei, Roma (1964).
[29] A. J. Birch, *XVII Internat. Congr. Pure and Appl. Chem.* Vol. 2; p. 73, Main Lectures, Munich (1959); Butterworths, London (1960).

Styryl monopyrone methyl ether (XI; R = Me)

Triacetic lactone methyl ether (X) (15 g) in methanol (150 ml) was added to magnesium methoxide in methanol (from 6 g magnesium powder in 300 ml methanol heated under reflux for 45 min). A solution of benzaldehyde (11·5 ml) in methanol (150 ml) was added dropwise and the stirred mixture was subsequently heated under reflux for 4 hr. The solvent was evaporated under reduced pressure and the residue acidified with 6N hydrochloric acid (100 ml), extracted with ethyl acetate (3 × 250 ml), and the extracts washed and dried. Removal of the solvent gave a yellow gum which was triturated with ether to yield styryl monopyrone methyl ether (XI; R = Me) (8 g; 33%). Crystallization from ethanol gave (XI; R = Me) as a pale yellow crystalline solid, m.p. 137–139°, lit.[13] m.p. 139–140°; λ_{max} 210, 225, 232, 254 and 344 mμ (ε 17,000, 13,000, 14,000, 11,000, 20,000; ν_{max} 1720, 1640, 1605, 1550 cm^{-1}; NMR bands (trifluoroacetic acid) 6·01 (3H, singlet), 4·03 (1H, doublet $J \sim 2$ c/s), 3·65 (1H, doublet $J \sim 2$ c/s), 3·25 (1H, doublet $J \sim 16$ c/s), 2·55 (5H, multiplet), 2·46 (1H, doublet $J \sim 16$ c/s); TLC, solvent A: R_f 0·80, solvent B: R_f 0·38.

Styryl monopyrone (XI; *R = H*)

Styryl monopyrone methyl ether (XI; R = Me) (10 g) in acetic acid (100 ml) containing 48% hydrobromic acid (30 ml) was heated on a steam bath for 20 min. Cooling the resultant solution and adding it slowly to ice water (800 ml) containing sodium bicarbonate (25 g) gave a dark orange precipitate which was filtered, washed with water and dried. The crude product was dissolved in hot ethyl acetate (1 l.), treated with charcoal, and the filtered solution concentrated in vacuo. Styryl monopyrone (XI; R = H) was obtained (6 g; 64%) as a yellow solid which was crystallized from ethyl acetate, m.p. 235–245° (decomp.), lit.[12] m.p. 245–246°; λ_{max} 225, 232, 256, 348 mμ (ε 17,200, 16,300, 14,000, 19,800); ν_{max} 1640, 1595, 1530 cm^{-1}; TLC, solvent A: R_f 0·20.

Styryl dipyrone (XII)

Styryl monopyrone (XI; R = H) (5 g) was dissolved in trifluoroacetic acid (75 ml). Malonyl dichloride (7 ml) was added dropwise and the solution heated under reflux for 2 hr. Addition of ethyl acetate (150 ml) to the cooled reaction mixture yielded a crude reaction product which on crystallization from $CHCl_3$ (charcoal) gave the styryl dipyrone (XII) as a yellow solid (3 g; 46%) m.p. 260–263° (decomp.); λ_{max} 232, 272, 392 mμ (ε 12,600, 10,300, 22,600); ν_{max} 1740, 1690, 1640, 1560 cm^{-1}; NMR bands (trifluoroacetic acid) at 4·11, 3·34, 3·09 (1H, doublet $J \sim 16$ c/s), 2·53 (5H, multiplet), 2·24 (1H, doublet $J \sim 16$ c/s). Molecular ion *m/e* 282 ($C_{16}H_{10}O_5$ requires 282·24); TLC, solvent A: R_f 0·63. $FeCl_3$: orange complex. Anal. Calc. for $C_{16}H_{10}O_5$: C, 68·08; H, 3·57. Found: C, 67·56; H, 3·75.

Phenethyl dipyrone (XIII)

Styryl dipyrone (680 mg) in ethyl acetate (600 ml) containing 30% palladium on charcoal (270 mg) was hydrogenated at room temperature and atmospheric pressure until one equivalent of hydrogen had been consumed. Filtration, evaporation of the solvent and crystallization from methanol yielded the dihydro derivative (600 mg, 88%) as a pale yellow solid, m.p. 175–177°: λ_{max} 270, 331 mμ (ε 12,500, 8700); ν_{max} 1750, 1690, 1615, 1565 cm^{-1}: NMR bands (trifluoroacetic acid) at 6·87 (4H, singlet), 4·07 (1H, singlet), 3·48 (1H, singlet), 2·73 (5H, singlet); TLC, solvent A: R_f 0·75. Molecular ion *m/e* value: 284; $C_{16}H_{12}O_5$ requires 284·26 $FeCl_3$ test: red complex.

Anal Calc for $C_{16}H_{12}O_5$: C, 67·60; H, 4·26 Found: C, 67·73; H, 4·15.

Reaction of styryl dipyrone (XII) *with magnesium methoxide: formation of* 8*-carbomethoxy*-5,7*-dihydroxy-flavanone* (XVII)

Styryl dipyrone (XII) (280 mg), as a slurry in methanol (50 ml) was added to magnesium methoxide in methanol (from 500 mg magnesium powder in 25 ml dry methanol heated under reflux for 30 min), and the resulting mixture was heated under reflux for 1 hr. After cooling, the solvent was removed under reduced pressure and the residue acidified to pH 2 with dilute hydrochloric acid, extracted with ethyl acetate (3 × 50 ml), washed with water (3 × 20 ml) and dried ($MgSO_4$). Removal of the solvent yielded a brown gum (370 mg) which, on trituration with ether, gave a yellow solid. Crystallization of the solid from benzene yielded 8-carbomethoxy-5,7-dihydroxyflavanone (XVII) as colourless prisms (40 mg, 13%), m.p. 178–179°; λ_{max} 255, 289, 325 mμ (ε 36,500, 10,300, 5000); ν_{max} 1655, 1640, 1610, 1580; NMR* bands

* Assignment confirmed by examination of the ABX portion of the spectrum at 100 Mc/s (Varian HA-100 spectrometer).

(deuterochloroform) at 7·0 (2H, octet AB position of ABX system, $J_{AB} \sim 17{\cdot}5$ c/s, $J_{AX} \sim 12$ c/s, $J_{BX} \sim 4$ c/s), 6·04 (3H, singlet), 4·56 (1H, quartet, X position of ABX system $|J_{AX} + J_{BX}|$ 16 c/s), 3·95 (1H, singlet), 2·58 (5H, singlet), −2·70 (1H, singlet), −3·97 (1H, singlet); TLC, solvent A: R_f 0·90, solvent B: R_f 0·70; molecular ion *m/e* value: 314 ($C_{17}H_{14}O_6$ requires 314·28); $FeCl_3$ test: red–brown complex; Gibbs test: negative. Anal. Calc. for $C_{17}H_{14}O_6$: C, 64·96; H, 4·49. Found: C, 65·12; H, 4·60.

Reaction of phenethyl dipyrone (XIII) *with magnesium methoxide: formation of the dihydrochalcone* (XX)

The reaction conditions described above for compound (XII) were used. Crystallization of the crude reaction product from benzene yielded 3-carbomethoxy-2,4,6-trihydroxydihydrochalcone (XX). (48 mg; 15%), m.p. 144–146°; λ_{max} 257, 285 (sh), 315 (sh) mμ (ε 33,200, 10,000, 3200); ν_{max} 1660, 1640, 1580 cm^{-1}; NMR bands (deuterochloroform) at 6·78 (4H, multiplet), 5·95 (3H, singlet, 4·00 (1H, singlet), 2·75 (5H, singlet), 0·37 (1H, broad), −2·2 (1H, broad), −4·33 (1H, singlet); TLC, solvent B: R_f 0·60; molecular ion *m/e* value: 316·0 ($C_{17}H_{16}O_6$ requires 316·30); $FeCl_3$ test: orange complex. Gibbs test: positive. Anal. Calc. for $C_{17}H_{16}O_6$: C, 64·55; H, 5·10. Found: C, 64·46; H, 5·22.

Reaction of styryl dipyrone (XII) *with methanolic potassium hydroxide: formation of stilbene derivatives* (*XVIa–c*)

Styryl dipyrone (XII; 1·0 g) was stirred under nitrogen with 1N methanolic KOH (650 ml) for 16 hr. The reaction mixture was concentrated *in vacuo* to small bulk, acidified to pH 2 with dilute hydrochloric acid, extracted with ethyl acetate (3 × 300 ml) and the extracts washed and dried. Removal of the solvent gave a brown gum (720 mg) which was separated into 3 fractions by acetone extraction of the appropriate bands on preparative TLC (20 × 60 cm plates, solvent B).

Fraction 1. Crystallization from cyclohexane gave 2-carbomethoxy-3-hydroxy-5-methoxystilbene (XVIa) as a colourless crystalline solid (48 mg, 8%), m.p. 138–140°C. λ_{max} 220, 319 mμ (ε 20,600, 36,400); ν_{max} 1650, 1610, 1580, 1560 cm^{-1}; NMR bands (deuterochloroform) at 6·08 (3H, singlet), 6·05 (3H, singlet), 3·46 (1H, doublet $J \sim 1{\cdot}5$ c/s), 3·23 (1H, doublet $J \sim 1{\cdot}5$ c/s), 2·98 (1H, doublet $J \sim 16$ c/s), 2·86 (1H, doublet $J \sim 16$ c/s), 2·6 (5H, multiplet), −1·59 (1H); TLC, solvent B: R_f 0·72; molecular ion *m/e* value 284 ($C_{17}H_{16}O_4$ requires 284·30); $FeCl_3$ test: brown complex. Anal. calc. for $C_{17}H_{16}O_4$: C, 71, 82; H, 5·67. Found: C, 72·11; H, 5·35.

Fraction 2. Crystallization from benzene yielded 2,4-carbomethyoxy-3,5-dihydroxystilbene (XVIb; 51 mg, 7%), m.p. 118–120°; λ_{max} 235 (sh), 255, 318 mμ (ε 15,000, 16,500, 27,500); ν_{max} 1660, 1610, 1560 cm^{-1}; NMR bands (deuterochloroform) at 6·07 (3H, singlet), 6·00 (3H, singlet, 3·27 (1H), 3·00 (1H, doublet $J \sim 16$ c/s), 2·71 (1H, doublet $J \sim 16$ c/s), 2·60 (5H, multiplet), −1·37 (1H), −2·23 (1H); TLC, solvent B: R_f 0·66; molecular ion *m/e* value: 328 ($C_{18}H_{16}O_6$ requires 328·31); $FeCl_3$: red complex. Repeated attempts to obtain satisfactory elemental analyses on this compound failed.

Fraction 3. Trituration with ether followed by crystallization from benzene yielded 2-carbomethoxy-3,5-dihydroxystilbene (XVIc; 75 mg, 13%) as a colourless solid, m.p. 161–162°; λ_{max} 219, 260, 300 mμ (ε 17,300, 30,000, 20,200); ν_{max} 1650, 1580 cm^{-1}; NMR bands (acetone) at 6·05 (3H, singlet), 3·62 (1H, doublet $J \sim 2{\cdot}5$ c/s); 3·32 (1H, doublet $J \sim 2{\cdot}5$ c/s), 3·09 (1H, doublet $J \sim 16$ c/s), 2·60 (5H, multiplet), 2·24 (1H, doublet $J \sim 16$ c/s), −1·5 (1H, broad); TLC, solvent B: R_f 0·33; $FeCl_3$ test: brown complex Calc. for $C_{16}H_{14}O_4$: C, 71·10; H, 5·22%). Found: C, 71·04; H, 5·15.

Treatment of phenethyl dipyrone (XIII) *with methanolic potassium hydroxide: formation of dihydrostilbenes* (XIXa–c)

Phenethyl dipyrone (XIII; 200 mg) was stirred under nitrogen with 1N KOH (100 ml) for 20 hr. The reaction mixture was worked up in the manner described in the preceding experimental and separated into three major fractions by extraction of appropriate bands on preparative TLC plates (solvent B) with ethyl acetate.

Fraction 1. This was obtained as a brown gum (35 mg). Further purification was achieved by preparative TLC (20 × 20 cm plate, solvent B), and extraction of the band with ethyl acetate yielded a dark yellow solid (15 mg) which was crystallized from n-hexane to yield 2,4-dicarbomethoxy-5-phenethylresorcinol (XIXc) m.p. 89–91°; λ_{max} 233, 245 (sh), 264 (sh), 319 mμ (ε 21,600, 18,000, 14,000, 5400); ν_{max} 1660, 1620, 1605, 1570 cm^{-1}; NMR bands (deuterochloroform) at 7·05 (4H, multiplet), 6·08 (3H, singlet), 5·99 (3H, singlet), 3·64 (1H, singlet), 2·77 (5H, singlet), −1·23 (1H), −2·15 (1H); TLC, solvent B: R_f 0·77. Highest *m/e* value 271 ($C_{18}H_{18}O_6$ requires 330·32; loss of CO_2Me provides 271), $FeCl_3$ test: red complex.

Fraction 2 (48 mg, 25%). Crystallization from benzene yielded 2-phenethyl-4-methoxysalicyclic acid

(XIXb), m.p. 156–159°; λ_{max} 221, 260, 302 mμ (ε 22,400, 11,800, 5300); ν_{max} 1625, 1615, 1570 cm^{-1}; NMR bands (acetone-d_6) at 6·90 (4H, multiplet), 6·22 (3H, singlet), 3·66 (2H, singlet), 2·78 (5H, singlet); TLC, solvent B: R_f 0·49; highest *m/e* value 228 ($C_{16}H_{16}O_4$ requires 272·29: loss of CO_2 provides 228). $FeCl_3$ test: dark brown complex. Anal. calc. for $C_{16}H_{16}O_4$: C, 70·57; H, 5·92. Found: C, 70·34; H, 5·93.

Fraction 3. This was obtained as a brown solid (29 mg) which was tentatively identified as 2-carbomethoxy-3-phenethylresorcinol (XIXa); λ_{max} 221, 265, 303 mμ (ε 18,000, 12,000, 5000); TLC, solvent B: R_f 0·23. $FeCl_3$ test: purple complex. Further work on this compound was hindered by difficulties in purification.

Treatment of phenethyl dipyrone (VII) *with aqueous potassium hydroxide*

The phenethyl dipyrone (VII; 500 mg) was heated under nitrogen on a steam bath with N potassium hydroxide (125 ml) for 15 min. After cooling, the solution was acidified to pH 2 with dilute hydrochloric acid and extracted with ethyl acetate. Working up in the usual way provided a brown oil (471 mg). The oil was separated into two major fractions by preparative TLC (20 × 60 cm plates, solvent A) and these were extracted from the plates with acetone.

Fraction 1. Evaporation of the acetone extract gave a red semi-solid (104 mg) which was crystallized from benzene to yield a pale pink crystalline solid. Recrystallization of the product from n-hexane:ethyl acetate (3:1) (after charcoal) was achieved at −80° to yield (XVIIIb) as a colourless crystalline solid, m.p. 140–142° (decomp.); λ_{max} 220, 262, 302 mμ (ε 20,000, 20,300, 4500); ν_{max} 2700, 2550, 1630, 1590, 1530 cm^{-1}; NMR bands (acetone -d_6) at 6·90 (4H, multiplet), 3·70 (1H, singlet), 3·67 (1H, singlet), 2·73 (5H, singlet); TLC solvent A: R_f 0·44. Highest neutralization equivalent 261 ± 5 ($C_{15}H_{14}O_4$ requires 258); *m/e* value 258. $FeCl_3$ test: purple complex. This material tended to decompose on crystallization and the two elemental analyses which were determined, provided inconclusive results.

Fraction 2. Removal of the solvent yielded a yellow gum (116 mg) which was purified initially by preparative TLC (20 × 20 cm plates, solvent A). The major band was extracted with acetone and after removal of the solvent this extract yielded a colourless solid which was tentatively identified as 5-phenethylresorcinol (XIVa). λ_{max} 232, 248 (sh), 255 (sh), 260 (sh), 262 (sh), 265 (sh), 269 (sh), 276, 283. (ε 2900, 320, 470, 670, 770, 920, 1200, 1500, 1500); TLC, solvent A: R_f 0·15. $FeCl_3$ test: negative. Insufficient material prevented further examination of this compound.

Reaction of dipyrone (XVII) *with methanolic magnesium methoxide*

Dipyrone (XVII; 1·0 g) as a slurry in methanol (250 ml) was added to magnesium methoxide in methanol (from 2·0 g of magnesium powder to methanol (100 ml) and heated under reflux for 30 min). The reaction mixture was refluxed for 1 hr, cooled, and the solvent removed under reduced pressure. The residue was acidified (pH 2) with dilute hydrochloric acid, extracted with ethyl acetate and the product isolated in the usual way. A yellow gum was obtained from which, after trituration with ether and crystallization of the residue from benzene (XXV; 99 mg, 8·5%) was obtained as colourless prisms, m.p. 137–138°; λ_{max} 256, 275 (sh), 317 (sh) (ε 37,000, 14,000, 4400); ν_{max} 2700 (w), 1650, 1630, 1610 (sh), 1570 cm^{-1}. NMR bands (acetone-d_6) at 7·35 (3H, singlet), 5·90 (3H, singlet), 4·11 (1H, singlet), −0·25 (1H), −2·73 (1H), −4·05 (1H). TLC, solvent A: R_f 0·75 and solvent B: R_f 0·48; molecular ion *m/e* value: 226 ($C_{10}H_{10}O_6$ requires 226·18); $FeCl_3$ test: purple complex. Anal. calc. for $C_{10}H_{10}O_6$; C, 53·10; H, 4·46. Found: C, 52·92; H, 4·18.

Condenation of triacetic acid lactone with benzaldehyde: formation of (XIV)[15,16]

Triacetic acid lactone (3 g), benzaldehyde (2·5 ml), pyridine (18 ml), piperidine (1 drop) and glacial acetic acid (1 drop) were heated on a steam bath for 4 hr. The reaction mixture was poured into cold 3N hydrochloric acid (70 ml) and the resinous material which formed was separated. To the mother liquor was added a further quantity of 3N hydrochloric acid (2 ml) and a floculent buff coloured precipitate which formed was filtered, washed and dried. Trituration of this solid with ether and several crystallizations from methanol yielded a white crystalline product (XIV) (20 mg), m.p. 208–212°, lit.[16] m.p. 215°; λ_{max} 1680, 1610, 1560, 1280 cm^{-1}; NMR bands (trifluoroacetic acid) at 7·60 (6H, singlet), 3·85 (1H, singlet), 3·55 (2H, singlet), 2·7 (5H, multiplet), TLC, solvent A:R_f 0·65. (Found: C, 67·89; H, 5·27. Calc. for $C_{19}H_{16}O_6$: C, 67·06; H, 4·74%). The resinous material which had been isolated was shown (TLC) to be a complex mixture of at least 7 components, including XXIII and was not examined further.

Conversion of (XVIa–c) *to pinosylvin* (VIII)

XVIa (120 mg) was treated with acetic acid (2 ml) and 48% hydrobromic acid (1 ml) and the mixture heated under reflux for 20 min. After cooling the mixture was poured into ice water (20 ml) and neutralized with sodium bicarbonate. Extraction with ethyl acetate and evaporation of the washed and dried extract yielded a brown oil (63 mg). TLC (solvent A) examination of this product revealed a major component whose R_f was identical to that of authentic pinosylvin. Further purification by preparative TLC (20 × 60 cm plates: solvent A) yielded a brown solid (11 mg) which on slow crystallization from acetone gave a colourless, crystalline solid, m.p. 155–157° (mixture m.p. with authentic pinosylvin: 155–157°); λ_{max} 300, 309 mμ (ε 29,000, 29,000); ν_{max}* 3390, 3260, 1620, 1600, 1590, 1500 cm^{-1}; NMR† bands (deuteroacetone) at 3·68 (1H, triplet $J \sim 2$ c/s), 3·42 (2H, doublet $J \sim 2$ c/s), 2·95 (2H, singlet), 2·60 (5H, multiplet), 1·78 (2H, broadened singlet); TLC, solvent A: R_f 0·22. The IR, UV, and NMR spectra were identical to those of authentic pinosylvin.

A mixture (250 mg) of (XVIb) and (XVIc) was heated under reflux for one hour with a solution of sodium hydroxide (180 mg) in methanol (1 ml) and water (4 ml). The cooled solution was neutralized (pH 6–7) with dilute hydrochloric acid and extracted with ethyl acetate. Evaporation of the solvent yielded a brown oil (180 mg) from which a brown solid (65 mg) was obtained by preparative TLC (see above).

This product was identical to that obtained from (XVIa) and was purified in the same way to yield a colourless solid, m.p. 155–157°, whose IR, UV and NMR spectra were identical to those of authentic pinosylvin.

Conversion of (XVII) *to pinocembrin* (IX)[6, 26]

8-Carbomethoxy-5,7-dihydroxyflavanone (XVII) (100 mg) was treated with 0·6N NaOH (5 ml) and the solution was heated under reflux for 1 hr. The cooled solution was acidified (pH 4) with 2N hydrochloric acid and extracted with ethyl acetate. Evaporation of the solvent yielded a yellow tar (83 mg) which contained a component whose R_f was identical to that of authentic pinocembrin. Purification by preparative TLC (20 × 40 cm plate: solvent A) yielded pale brown crystals (18 mg, 22%) which on recrystallization from benzene:ethyl acetate (3:1) gave a colourless, crystalline solid m.p. 198–200°); λ_{max}‡ 214, 228 (sh), 290, 325 (sh) mμ (ε 21,300, 15,100, 16,600, 4400); ν_{max}§ 1630, 1605, 1580 cm^{-1}; NMR‖ bands (deuterochloroform) at 7·08 (2H, AB portion of ABX system, $J_{AB} = 17·5$ c/s, $J_{AX} = 12·5$ c/s, $J_{BX} = 4$ c/s), 4·63 (1H, X portion of ABX system, $J_{AX} + J_{BX} = 16·5$ c/s), 4·36 (1H, broad), 4·05 (2H, singlet), 2·60 (5H, singlet), −2·00 (1H, singlet); TLC, solvent A: R_f 0·50, solvent B: R_f 0·13; $FeCl_3$ test: positive (red-brown); Gibbs test: positive (red). The IR, UV and NMR spectra were identical to those of authentic pinocembrin.

Acknowledgements—We are grateful to the National Research Council of Canada for financial support (NRC A2267) and for an N.R.C. Scholarship (J.L.D.)

* Determined on a Perkin-Elmer Model 237 spectrometer as a Nujol mull.

† Determined on a Varian HA-100 spectrometer at 100 Mc/s and on a Varian A-60 spectrometer at 60 Mc/s.

‡ Determined on a Unicam SP.800 spectrometer in methanol.

§ Determined on a Perkin-Elmer Model 237 spectrometer as a Nujol mull.

‖ Determined on a Varian HA-100 spectrometer at 100 Mc/s.