Tetrahedron. Vol. 27, pp. 1043–1048. Pergamon Press 1971. Printed in Great Britain

THE NATURAL OCCURRENCE OF 6-STYRYL-2-PYRONES AND THEIR SYNTHESIS[1]

A. M. BITTENCOURT, O. R. GOTTLIEB, W. B. MORS and M. TAVEIRA MAGALHÃES
Instituto de Tecnologica Agricola e Alimentar, Ministério da Agricultura, Rio de Janeiro, Brasil

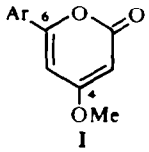
and

S. MAGESWARAN, W. D. OLLIS and I. O. SUTHERLAND
Department of Chemistry, The University, Sheffield S3 7HF, England

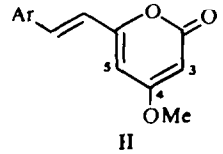
(*Received in the UK* 28 *September* 1970; *Accepted for publication* 7 *October* 1970)

Abstract—Three representatives of a new type (IV) of natural 6-styryl-2-pyrones have been isolated from the wood of *Aniba parviflora* (Meissn.) Mez. Their constitutions (IVa, IVb, and IVc), proposed mainly on spectroscopic evidence, have been confirmed by synthesis.

THE aromatic derivatives of monocyclic 2-pyrones[2,3] are phytochemically associated with *Aniba* species[1] (Lauraceae) and the known natural 2-pyrones isolated from this source have been distributed[2] among three general types (I, II, and III). These three types are associated with either an aryl or a styryl (Ar—CH=CH—) substituent in position 6, and the presence or the absence of a OMe group in position 4. Biogenetic analysis indicates[4] that these natural products are derivable by the polyketide route involving initiation either by benzoic acids leading to the 6-aryl-2-pyrones (I and III) or by cinnamic acids leading to the 6-styryl-2-pyrones (II). The absence of a 4-OMe substituent in the 6-aryl-2-pyrones (III) may well be associated with a reductive deoxygenation at the polyketide stage and the natural occurrence of 6-styryl-2-pyrones (IV) could be expected. We now report[5] upon the isolation of 6-styryl-2-pyrones of this type (IV) and a general route for their synthesis.



I



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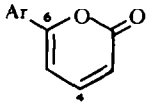
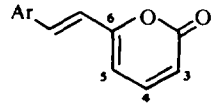


III



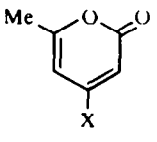
IV

a: Ar = phenyl
b: Ar = 3′,4′-methylenedioxyphenyl
c: Ar = 4′-hydroxy-3′-methoxyphenyl
d: Ar = 3′,4′-dimethoxyphenyl

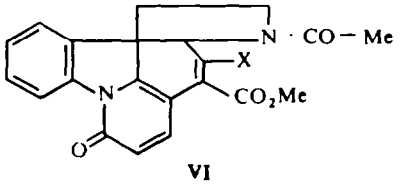
The plant material was collected from a tree identified as *Aniba parviflora* (Meissn.) Mez. growing in the dense forest near Santarém in the Amazon valley. Extraction of the wood and chromatographic fractionation yielded four natural products, of which three were new. The fourth was identified as 4-methoxyparacotoin (Ib) which has been previously isolated from several *Aniba* species, including *A. duckei* Kosterm.,[6] *A. rosaeodora* Ducke.[6] *A. fragrans* Ducke.[7] and *A. firmula* (Nees and Mart.) Mez.[8]

The general constitutional features of the new compounds: (i) $C_{13}H_{10}O_2$, yellow crystals, m.p. 115–116°; (ii) $C_{14}H_{10}O_4$, yellow crystals, m.p. 173–175°; and (iii) $C_{14}H_{12}O_4$, orange crystals, m.p. 159–160°, were clearly indicated by their UV, IR, and NMR spectra. Their IR spectra showed absorption in the CO region (ν_{max} ~ 1720 cm^{-1}) compatible with their formulation as 2-pyrones[2, 9, 10] and their UV spectra were highly reminiscent of the chromophoric properties[2, 10] of the natural 4-methoxy-6-styryl-2-pyrones (III). This was supported by the presence in their IR spectra of bands (ν_{max} ~ 1640 and ~960 cm^{-1}) indicating the presence of a *trans*-disubstituted ethylene associated with a styrenoid residue.[2] Compound (i) also showed absorption (ν_{max} 770 and 702 cm^{-1}) compatible with the presence of a phenyl group, and compound (iii) showed hydroxyl absorption (ν_{max} 3360 cm^{-1}). A relationship between the compounds (i), (ii), and (iii) was established by their oxidation with potassium permanganate: compound (i) yielded benzoic acid, compound (ii) gave piperonylic, and compound (iii) gave with diazomethane a monomethyl derivative, which yielded veratric acid by a similar oxidation. These results, in association with their molecular formulae, suggested the formulation of compounds (i), (ii), and (iii) as the 6-styryl-2-pyrones (IVa, IVb, and IVc) respectively. The relative orientation of the OMe and OH substituents in the compound IVc was indicated by a negative Gibbs' test.[11]

The constitutions IVa, IVb, and IVc were also clearly indicated by their NMR spectra. These showed an AB system (τ_A ~ 2·6, τ_B ~ 3·6, J_{AB} = 16 Hz) assignable to the *trans*-disubstituted ethylene of the styrenoid type very similar to the AB-system already described[12] for several 4-methoxy-6-styryl-2-pyrones (II). Compounds of the type II also show another AB system (τ_A ~ 4·0, τ_B ~ 4·5, J_{AB} ~ 2 Hz) assignable to the 3-H and 5-H of the 2-pyrone residue.[12] In contrast, compounds of the type IV are easily recognized, since their NMR spectra show ABX systems (τ_A ~ 3·9, τ_B ~ 3·8, τ_X ~ 2·7; J_{AB} = 0, J_{AX} ~ 7, J_{BX} ~ 9Hz) assignable to the 3-H, 5-H, and 4-H respectively of the 2-pyrone residue (IV).



V



VI

a: X = OH; b; X = O-Tosyl; c: X = SCH_2Ph; d: X = H; e: X = OMe

This recognition of the 6-styryl-2-pyrones (IVa, IVb, and IVc) as representatives of a further class of natural 2-pyrones, in accord with biogenetic expectation, encouraged the search for a route that would be a general method for their synthesis. The approach which was envisaged was based upon the method already developed[10] for the synthesis of

the natural 2-pyrones of the type II. This involves the base-catalysed condensation between 4-methoxy-6-methyl-2-pyrone (Ve) and aromatic aldehydes, so the corresponding route to compounds of the type IV therefore required 6-methyl-2-pyrone (Vd) as an intermediate.

Published methods for the synthesis of 6-methyl-2-pyrone (Vd) are not very satisfactory. It was first obtained[13] as a by-product (0·2% yield) during the catalytic hydrogenation of hexa-2,4-diynoic acid. The direct reductive transformation of the O-diethyl phosphate[14] of 4-hydroxy-6-methyl-2-pyrone (Va) could not be achieved,[15] but van Dam and Kögl[15] described an acceptable synthesis of 6-methyl-2-pyrone (Vd; 49% yield) by reduction of its 4-chloro-derivative with zinc and hydrochloric acid. Another route to 6-methyl-2-pyrone (Vd) from 1,1-dichloro-1,3-hexadiene-5-one prepared from acetone and 1,1,3-trichloro-3-ethoxyprop-1-ene has been described.[16, 17]

This situation encouraged further examination of possible synthetic routes to 6-methyl-2-pyrone (Vd) from the readily available[18] 4-hydroxy-6-methyl-2-pyrone (triacetic acid lactone) (Va). This reductive transformation has now been satisfactorily achieved by the sequence (Va→Vb→Vc→Vd). The O-tosylate (Vb), obtained from the 4-hydroxy-6-methyl-2-pyrone and toluenesulphonyl chloride in pyridine, reacted smoothly with sodium benzylmercaptide in methanol yielding the benzyl thio-ether (Vc). This substitution at position 4 involves a sequence of nucleophilic β-addition followed by a β-elimination. The benzylthio-ether (Vc) was then smoothly desulphurized with deactivated Raney nickel yielding the required 6-methyl-2-pyrone. This reductive sequence is entirely analogous to transformations (VIa→VIb→VIc→VId) used in the total synthesis of strychnine.[19]

The base-catalysed condensation between aromatic aldehydes and the 6-methyl-2-pyrone (Vd) could not be achieved using magnesium methoxide as the basic catalyst. Some 6-styryl-2-pyrone (IVa) was isolated using potassium t-butoxide in dimethyl formamide solution, but satisfactory condensations were achieved by heating 6-methyl-2-pyrone (Vd) with aromatic aldehydes and anhydrous sodium acetate. By this method, the compounds IVa, IVb, and IVd were obtained, thus confirming the constitutions IVa, IVb, and IVc of these three new natural 6-styryl-2-pyrones. 6-Styryl-2-pyrone (IVa) has also been synthesized[16] by acid-catalysed cyclization of $PhCOCH{=}CH{-}CH{=}CCl_2$ prepared by condensation of acetophenone with 1,1,3-trichloro-3-ethoxy-prop-1-ene.

EXPERIMENTAL

UV spectra were measured in 95% EtOH. IR spectra were, unless otherwise indicated, determined using $CHCl_3$ solns and only significant bands are quoted. NMR spectra were determined either at 60 or 100 MHz using $CDCl_3$ solns with TMS as the internal standard. The multiplicities of NMR signals are quoted as s = singlet, d = doublet, dd = double doublet, and m = multiplet.

M.ps were determined using a Kofler hot stage microscope and are uncorrected.

Separations by column chromatography were carried out, unless otherwise indicated, using Hopkins and Williams' MFC grade silica. Merck Kieselgel G was used for thick and thin layer chromatography (TLC). During isolation processes, the combination of appropriate fractions was determined by examination of their IR spectra and TLC behaviour.

All evaporations were carried out under diminished pressure.

Identity of compounds was established by comparison of m.p., mixed m.p., IR spectra, and, where appropriate, NMR and mass spectra.

Extraction of the wood of Aniba parviflora *(Meissn.) Mez.*

Isolation of 4-methoxyparacotoin (Ib), *6-styryl-2-pyrone* (IVa), *6-(3′,4′-methylenedioxystyryl)-2-pyrone*

(IVb), 6-(*4'-hydroxy-3'-methoxystyryl*)-2-*pyrone* (IVc). The powdered wood (5Kg) was continuously extracted with hot benzene. Concentration and cooling gave a solid (A) which was collected. The benzene filtrate was shaken with NaOH aq (3%) and after washing with water, evaporation of the benzene layer gave fraction B. Acidification of the alkaline extract, extraction with $CHCl_3$ and evaporation gave fraction C.

A was dissolved in $CHCl_3$, filtered through a silica column, evaporated, and crystallized from light petroleum (b.p. 40–60°) yielding 6-*styryl*-2-*pyrone* (IVa; 10g).

B was chromatographed on alumina (Brockmann-deactivated by treatment with 10% aqueous AcOH). Elution with benzene gave three crystalline fractions (B_1, B_2, and B_3). Recrystallization of B_1 from light petroleum (b.p. 40–60°) gave 6-styryl-2-pyrone (IVa; 1·5 g). Recrystallization of B_2 from EtOH—$CHCl_3$ (2 : 1 v/v) gave 6-(3', 4'-*methylenedioxystyryl*)-2-*pyrone* (IVb; 55 mg). Recrystallization of B_3 from EtOH gave 4-methoxyparacotoin (Ib; 12 mg).

C was dissolved in $CHCl_3$, filtered through a silica column, evaporated, and recrystallized from EtOH—benzene (2 : 1 v/v) yielding 6-(*4'-hydroxy-3'-methoxystyryl*)-2-*pyrone* (IVc; 45 mg).

Extraction of the bark of A. parviflora. The bark (50 g) similarly yielded 6-styryl-2-pyrone (IVa; 20 mg).

The identification of the extractives of Aniba parviflora

6-*Styryl*-2-*pyrone* (IVa), yellow crystals, m.p. 115–116° (Found: C, 78·8; H, 5·2. $C_{13}H_{10}O_2$ requires: C, 78·8; H, 5·1%); ν_{max} (KBr) 1733, 1637, 1603, 972, 770, 704 cm^{-1}.

6-(3' 4'-*Methylenedioxystyryl*)-2-*pyrone* (IVb), yellow crystals, m.p. 173–175° (Found: C, 69·3; H, 4·0. $C_{14}H_{10}O_4$ requires: C, 69·4; H, 4·2%); ν_{max} (KBr) 1724, 1637, 1613, 954 cm^{-1}.

6-(*4'-Hydroxy-3'-methoxystyryl*)-2-*pyrone* (IVc), orange crystals, m.p. 159–160° (Found: C, 68·5; H, 5·1. $C_{14}H_{12}O_4$ requires: C, 68·8; H, 5·0%); ν_{max}(KBr) 3360, 1709, 1639, 1613, 962 cm^{-1}.

4-Methoxyparacotoin (Ib), white needles, m.p. 222–224° (lit.[6] 222–224°) which was identical with an authentic sample.[6]

6-(3',4'-*Dimethoxystyryl*)-2-*pyrone* (IVd). Natural 6-(4'-hydroxy-3'-methoxystyryl)-2-pyrone (20 mg), dimethyl sulphate (0·5 ml), and anhyd K_2CO_3 (500 mg) in acetone (10 ml) were heated (8 hr) under reflux, cooled, filtered, and the filtrate evaporated. The residue was dissolved in benzene and filtered through a column of alumina (Brockmann-deactivated by treatment with 10% AcOH). Evaporation of the eluate and crystallization from light petroleum (b.p. 40–60°) gave 6-(3', 4'-dimethoxystyryl)-2-pyrone (12 mg) as yellow crystals, m.p. 98–100°; ν_{max}(KBr) 1724, 1647, 1616, 972 cm^{-1}.

Oxidation of the natural 6-*styryl*-2-*pyrones* (IVa, IVb, and IVc). 6-Styryl-2-pyrone (IVa; 30 mg) was dissolved in acetone (5 ml) and a saturated soln of $KMnO_4$ in acetone was added dropwise at room temp until a pink colour persisted. Sodium dithionite was then added and the mixture was filtered. Evaporation, addition of water, acidification and extraction with benzene gave an extract which was shaken with $NaHCO_3$ aq. Acidification of the bicarbonate extract followed by $CHCl_3$ extraction, evaporation, and sublimation of the residue under diminished pressure gave benzoic acid (5 mg), m.p. and mixed m.p. 121°.

Similarly, oxidation of IVb gave 3,4-methylenedioxybenzoic acid, and IVc gave 3,4-dimethoxybenzoic acid, by oxidation of its methyl ether (IVd).

Synthesis of the 6-*styryl*-2-*pyrones* (IVa, IVb, *and* IVd)

4-*Hydroxy*-6-*methyl*-2-*pyrone* (Va; *triacetic acid lactone*). The published method[18] gave 4-hydroxy-6-methyl-2-pyrone as colourless needles, m.p. 186–188° (lit.[18] 188–189°); λ_{max} 285 nm (ε 5860); ν_{max} 1770 and 1575 cm^{-1}; NMR spectrum: τ 4·03 m (5–H); τ 4·69 d (J = 2 Hz, 3-H); τ 6·7 br s (OH); τ 7·83 s (CH_3).

6-*Methyl*-4-*tosyloxy*-2-*pyrone* (Vb). A mixture of 4-hydroxy-6-methyl-2-pyrone (35 g) and *p*-toluenesulphonyl chloride (100 g) in pyridine (100 ml) was set aside at room temp (18 hr) and then poured into cold 5N HCl. Extraction with ether (4 × 500 ml), evaporation, and crystallization from EtOH gave 6-*methyl*-4-*tosyloxy*-2-*pyrone* (73 g) as pale yellow needles, m.p. 102° [Found: C, 55·4; H, 4·3; S, 11·5; M (mass spectrum), 280. $C_{13}H_{12}O_5S$ requires: C, 55·7; H, 4·3; S, 11·4%; M, 280]; λ_{max} 229 nm (ε 9630), 298 nm (ε 3850); ν_{max} 1745, 1640, 1575, 1380, 970 cm^{-1}; NMR spectrum: τ_X 3·18 d, τ_Y 3·61 d (A_2X_2 system, J_{AX} = 8·5 Hz, Me—$C_6H_4SO_2^-$); τ_A 4·18 d, τ_B 4·00 d (AB system, J_{AB} = 2 Hz, pyrone 3-H_A and 5-H_B); τ 7·53 (CH_3—$C_6H_4SO_2^-$); τ 7·77 s (6-CH_3).

4-*Benzylthio*-6-*methyl*-2-*pyrone* (Vc). Small pieces of Na (5·5 g) were added to a stirred soln of benzylthiol (30 g) in MeOH (1000 ml) (N_2 atm). After the Na had dissolved, 6-methyl-4-tosyloxy-2-pyrone (64 g) was added and the mixture was heated under reflux until soln occurred. After cooling, water was added, and $CHCl_3$ extraction (3 × 500 ml), evaporation, and crystallization of the residue from EtOH yielded 4-*benzylthio*-6-*methyl*-2-*pyrone* (32·0 g) as colourless plates, m.p. 89° [Found: C, 67·1; H, 5·2; S,

13·9; M (mass spectrum), 232. $C_{13}H_{12}O_2S$ requires: C, 67·2; H, 5·2; S, 13·8%; M, 232]; λ_{max} 223 nm (ε 18,400), 275 nm (ε 14·300), 303 nm (ε 7540); ν_{max} 1700, 1630 cm^{-1}; NMR spectrum: τ 2·68 s ($C_6\underline{H}_5$); τ 4·14 s (5-$\underline{H}$); τ 4·17 s (3-$\underline{H}$); τ 5·89 s ($C\underline{H}_2S$); τ 7·84 s (6-$C\underline{H}_3$).

6-Methyl-2-pyrone (Vd). Raney Ni prepared[20] from Ni-Al alloy (150 g) was deactivated by heating (3 hr) under reflux with acetone and then heating (3 hr) under reflux with EtOAc. A soln of 4-benzylthio-6-methyl-2-pyrone (20 g) in EtOH (500 ml) was then added to a suspension of the deactivated Raney Ni in EtOH (1000 ml) and the mixture was heated (5 hr) under reflux with vigorous stirring. The mixture was then filtered and the Raney Ni well washed with hot EtOH (3 x 150 ml). Evaporation of the combined filtrate and washings and distillation of the residue gave 6-methyl-2-pyrone (7·5 g) as a colourless oil, b.p. 102–106°/12mm (lit.[16, 17] b.p. 102–104°/17mm). [Found: M (mass spectrum), 110. Calc. for $C_6H_6O_2$: M, 110]; λ_{max} 218 nm (ε 2940), 302 nm (ε 7520); ν_{max} (liquid) 1725, 1640, 1090, 855, 790, 720 cm^{-1}; NMR spectrum: τ_A 4·05 d, τ_B 3·99 d, τ_X 2.79dd (ABX system, $J_{AB}=0$ Hz, $J_{AX}=6$ Hz, $J_{BX}=9$ Hz; pyrone 3-$\underline{H}_A$, 5-$\underline{H}_B$, 4-$\underline{H}_X$); τ 7·78 s (6-$C\underline{H}_3$).

6-Styryl-2-pyrone (IVa). 6-Methyl-2-pyrone (220 mg), benzaldehyde (220 mg), and freshly fused NaOAc (150 mg) were heated (oil bath temp 175–180°) for 9 hr, cooled, and water was added. EtOAc extraction (3 x 25 ml), evaporation, fractionation of the residue by thick layer chromatography (silica—$CHCl_3$), followed by crystallization from light petroleum (b.p. 40–60°) gave 6-styryl-2-pyrone (52 mg), m.p. 115–116° [Found: C, 78·5; H, 5·1; M (mass spectrum), 198. Calc. for $C_{13}H_{10}O_2$: C, 78·8; H, 5·1%; M, 198]; λ_{max} 237 nm (ε 9130), 243 nm sh (ε 8550), 265 nm sh (ε 11,900), 271 nm (ε 12,000), 367 nm (ε 21,600), 380 nm inf (ε 17,100); ν_{max} 1718, 1635, 962 cm^{-1}; NMR spectrum: τ 2·43–2·78 m ($C_6\underline{H}_5$—$C\underline{H}$= and pyrone 4-$\underline{H}$) τ 3·40 d ($J=16$ Hz, PhC$\underline{H}$=C$\underline{H}$—); τ 3·80 d ($J=9·5$ Hz, 5-$\underline{H}$); τ 3·88 d ($J=6$ Hz, 3-$\underline{H}$). It was identical with the natural product.

6-(3′,4′-Methylenedioxystyryl)-2-pyrone (IVb). 6-Methyl-2-pyrone (770 mg), piperonaldehyde (1·06 g) and NaOAc (600 mg) similarly yielded IVb (316 mg), m.p. 173–175° [Found: C, 69·0; H, 4·1; M (mass spectrum), 242. Calc. for $C_{14}H_{10}O_4$: C, 69·4; H, 4·1%; M, 242]; λ_{max} 230 nm inf (ε 9800), 237 nm inf (ε 470), 260 nm (ε 7600), 270 nm inf (ε 7200), 278 nm sh (ε 6400), 383 nm (ε 17,500); ν_{max} 1712, 1620, 960 cm^{-1}; NMR spectrum: τ_A 2·62 d, τ_B 3·58 d (AB system, $J_{AB}=16$ Hz, Ar—C$\underline{H}_A$=C$\underline{H}_B$—); τ_A 3·94 d, τ_B 3·84 d, τ_X 2·78 dd (ABX system, $J_{AB}=0$ Hz, $J_{AX}=7$ Hz, $J_{BX}=9$ Hz; pyrone 3-$\underline{H}_A$ 5-$\underline{H}_B$, and 4-$\underline{H}_X$); τ_A 3·03 d, τ_B 3·06 dd, τ_X 3·24 d (ABX system, $J_{AB}=2$ Hz, $J_{AX}=0$ Hz, $J_{BX}=9$ Hz, aromatic 2′-$\underline{H}_A$, 6′-$\underline{H}_B$, and 5′-$\underline{H}_X$); τ4·04 s ($C\underline{H}_2O_2$). It was identical with the natural product.

6-(3′,4′-Dimethoxystyryl)-2-pyrone (IVd). 6-Methyl-2-pyrone (220 mg), 3,4-dimethoxybenzaldehyde (340 mg), and NaOAc (160 mg) similarly yielded 6-(3′,4′-*dimethoxystyryl*)-2-*pyrone* (IVd; 50 mg), m.p. 98° [Found: C, 70·0; H, 5·6; M (mass spectrum), 258. $C_{15}H_{14}O_4$ requires: C, 69·8; H, 5·5%; M, 258]; λ_{max} 223 inf (ε 14,500), 229 nm inf (ε 13,700), 261 nm (ε 11,400), 270 nm inf (ε 11,200), 278 nm sh (ε 10,800), 385 nm (ε 24,500); ν_{max} 1715, 1630, 960 cm^{-1}; NMR spectrum: τ_A 2·56 d, τ_B 3·52 d (AB system, $J_{AB}=16$ Hz, ArC$\underline{H}_A$=C$\underline{H}_B$—); τ_A 3·91 d, τ_B 3·83 d, τ_X 2·70 dd (ABX system, $J_{AB}=0$ Hz, $J_{AX}=6·5$ Hz, $J_{BX}=9$ Hz; pyrone 3-$\underline{H}_A$, 5-$\underline{H}_X$); τ_A 2·97 d, τ_X 2·91 dd, τ_A 3·15 d (ABX system, $J_{AB}=2$ Hz, $J_{AX}=0$ Hz, $J_{BX}=8$ Hz; aromatic 2′-$\underline{H}_A$, 6′-$\underline{H}_B$, 5′-$\underline{H}_X$); τ 6·11 s (two $OC\underline{H}_3$). It was identical with the monomethyl ether (IVd) of the natural product (IVc).

Acknowledgements—We wish to thank the Conselho Nacional de Pesquisas, Brasil, for financial aid, the University of Ceylon for a grant to S. M., and Mr. Apparicio Pereira Duarte for the collection and identification of the plant material.

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