Intramolecular Oxidative Cyclisation of 1-(4-Hydroxyaryl)-2-ketoximes 4-HOArCH$_2$C(=NOH)R with Phenyliodine(III) Bis(trifluoroacetate)

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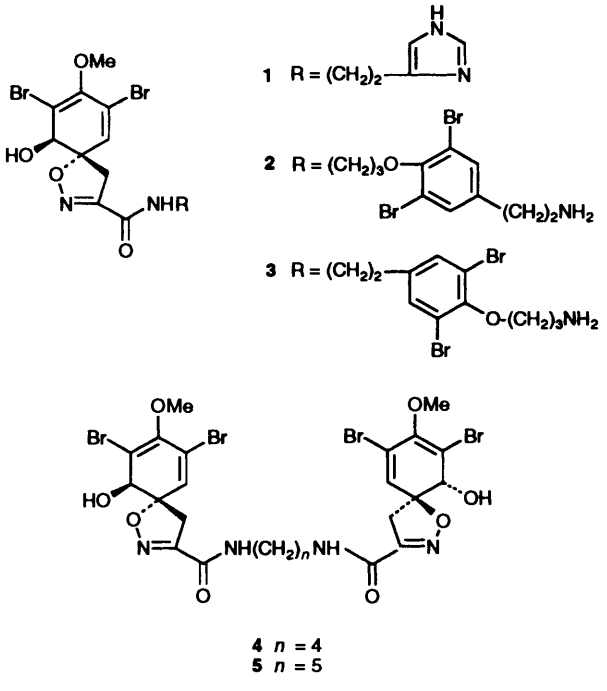
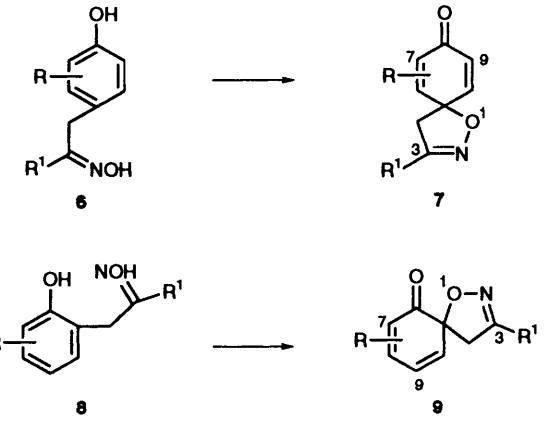
Reaction of 1-(4-hydroxyaryl)-2-ketoximes, 4-HOArCH$_2$C(=NOH)R, with phenyliodine(III) bis(trifluoroacetate) in acetonitrile at 0 °C results in smooth intramolecular oxidative cyclisation and formation of 1-oxa-2-azaspiro[4.5]deca-2,6,9-trien-8-ones in good to excellent yield. Attempted application of the procedure to 1-(2-hydroxyphenyl)propan-2-one oxime resulted in formation of the [4 + 2] dimer of the initially formed spiroisoxazoline.

During the last 20 years there have been numerous reports of the isolation and structure determination of 'dibromotyrosine derived' marine metabolites such as aerophobin 1 **1**,[1] the hexadellins A **2** and B **3**,[2] aerothionin **4** and homoaerothionin **5**,[3] which contain either one or two spirocyclohexadienyl-



isoxazoline subunits. Synthetic work on these natural products, little so far, has been concentrated largely on methods for spiroisoxazoline formation and a number of reagents have been examined for intramolecular oxidative cyclisation of oximes of types **6** and **8**.

In a series of model studies, Forrester *et al.* examined the reactions of a range of oximes **6** with lead(IV) acetate, potassium ferricyanide, silver oxide, sodium periodate, Fremy's salt and manganese tris(acetylacetonate).[4] The manganese reagent was found to be by far the most effective of these formal one or two electron oxidants, and yields of 19–60% of **7** were obtained. Sodium periodate, silver oxide, Fremy's salt and alkaline ferricyanide failed to effect spirocyclisation; use of lead(IV) acetate did give a spiroisoxazoline in one case, but in only 10% yield. In a subsequent study, the same workers showed that oxidation of **6** (R=H, R^1=CO$_2$Me) with bromine water resulted in both electrophilic bromination and spirocyclisation to give **7** (R=7,9-Br$_2$, R^1=CO$_2$Me) in 65% yield, while use of NBS with **6** (R=2,6-di-Bu^t, R^1=Me) gave **7** (R=7,9-di-Bu^t, R^1=Me) in



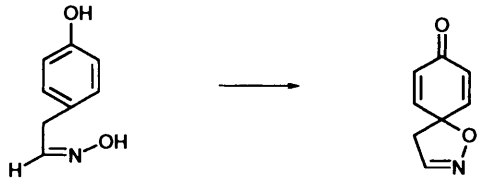
72% yield.[5] Oxidation of **6** (R=2,6-Br$_2$, R^1=CO$_2$Me) with thallium(III) nitrate in methanol was studied by Yamamura.[6] A mixture of products was obtained, which included 7–11% of **7** (R=7,9-Br$_2$, R^{1}CO$_2$Me). Intriguingly, Yamamura reported that the same transformation could be carried out in quantitative yield by anodic oxidation.

The cyclisation **8**→**9** has been studied to a much lesser degree. Forrester *et al.* found that of all the oxidants they examined, only 2,4,4,6-tetrabromocyclohexa-2,5-dienone would convert **8** (R=2,4-di-Bu^t, R^1=Me) into **9** (R=7,9-di-Bu^t, R^1=Me), but only in 20% yield.[5] An equally low yield of 27% was obtained by Yamamura on oxidation of **8** (R=2-OH, 3,5-Br$_2$, 4-OMe, R^1=CO$_2$Me) to **9** (R=7-HO, 8,10-Br$_2$, 9-OMe, R^1=CO$_2$Me) with thallium(III) trifluoroacetate in trifluoroacetic acid.[7]

There has been considerable interest recently in the use of hypervalent iodine compounds as electrophilic oxidants, and they have been used for the synthesis of many 4,4-disubstituted cyclohexa-2,5-dienones,[8] including a variety of spirocyclic systems formed by intramolecular oxidative cyclisation of 4-substituted phenols.[8–13] We now report the results of an investigation of the utility of phenyliodine(III) bis(trifluoroacetate) (PIFA) for cyclisations of the types **6**→**7** and **8**→**9**.

Results and Discussion

Oximation of 4-hydroxyphenylacetaldehyde gave a mixture of *syn* and *anti* oximes (NMR). Treatment of the mixture with PIFA in acetonitrile at 0 °C resulted mainly in tar formation and iodobenzene and some unchanged oxime were the only compounds that could be isolated from the black reaction mixture. Intramolecular oxidative cyclisation should be favoured for the *anti* oxime, and hence attempts were made to obtain this isomer pure. Recrystallisation of the mixture of



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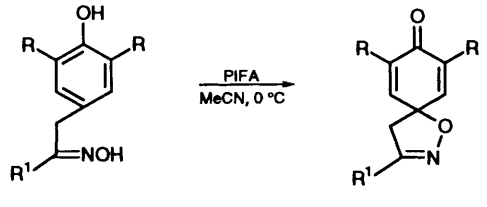
oximes from light petroleum–dichloromethane gave the pure *syn* isomer, but the desired, less stable *anti* isomer was always obtained as a mixture with the *syn* oxime. Attempted *syn*→*anti* isomerisation by treatment with hydrogen chloride in ether gave the hydrochloride salt, but reaction of this with saturated sodium hydrogen carbonate solution merely resulted in regeneration of 4-hydroxyphenylacetaldehyde. Treatment of the pure *syn* oxime with boron trifluoride instead of hydrogen chloride in a procedure recommended by Hauser and Hoffenberg[14] still gave a mixture of *syn* and *anti* isomers.

As the desired *anti* oxime **10** could not be obtained pure, thermal isomerisation was attempted prior to oxidation with PIFA. Thus, the *syn*, *anti* mixture of oximes was heated in acetonitrile for 5 min, then PIFA was added. This still resulted in much tar formation, but 1-oxa-2-azaspiro[4.5]deca-2,6,9-trien-8-one **11** was readily isolated in 20% yield by column chromatography. Iodobenzene and 4-hydroxybenzyl cyanide were also obtained. The low yield of **11** obtained under these conditions probably indicates that, as expected, the *anti* oxime **10** is the minor component of the oxime mixture even at equilibrium. It was thought that use of a ketoxime might circumvent or at least minimise the stereochemical problem associated with the aldoxime, and this proved to be the case. Thus, a series of ketoximes **12** was prepared and treated with PIFA in acetonitrile at 0 °C. Intramolecular oxidative cyclisation occurred smoothly and rapidly to give the corresponding spirocyclic isoxazolines **13** in good to excellent yield (Scheme 1). PIFA is clearly a very efficient reagent for this transformation.

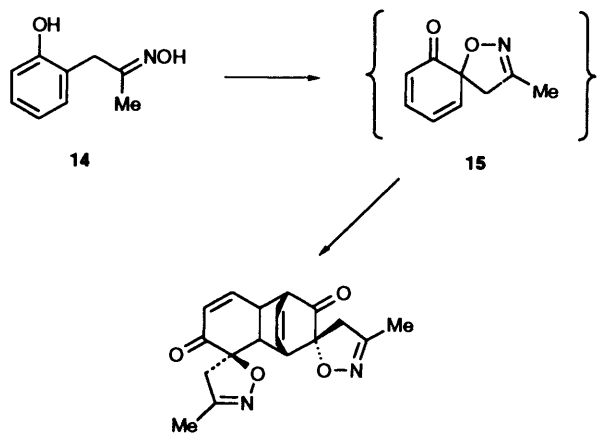


12 13

	R	R^1	Yield of **13** (%)
a	H	Me	63
b	Br	Me	58
c	H	Et	68
d	Br	Et	52
e	H	CMe_3	93
f	Br	CMe_3	89
g	H	CO_2Me	65
h	Br	CO_2Me	58
i	H	C_6H_5	86
j	Br	C_6H_5	78
k	H	$4\text{-}BrC_6H_4$	82
l	Br	$4\text{-}BrC_6H_4$	77

Scheme 1

Having established that PIFA is an effective reagent for the intramolecular oxidative cyclisation of the 4-hydroxyphenyl ketoximes **12**, attention was turned to the 2-hydroxyphenyl compounds. (2-Hydroxyphenyl)propane-2-one oxime **14** was taken as a test substrate (Scheme 2). Oxidation of **14** with PIFA



14 15 16

Scheme 2

in acetonitrile at 0 °C proceeded smoothly, and a colourless crystalline solid was isolated in 45% yield. It was immediately obvious from the IR, ^1H, ^{13}C and mass spectra, however, that this was a Diels–Alder dimer of the expected spirocyclic isoxazoline **15**. Four regioisomeric dimers of **15** are possible, each of which can give rise to diastereoisomeric products depending on the orientation of the two spiro units. It was not possible to assign a unique structure for the dimer on the basis of NMR data, but X-ray analysis showed the product to be **16**.* While formation of **16** is not unexpected,[15] the result of the PIFA oxidation **14**→**15**→**16** contrasts sharply with that obtained by Forrester when **14** was oxidised with manganese tris(acetylacetonate).[4] In that case, a mixture of 2-methylbenzofuran and (2-hydroxyphenyl)propan-2-one was obtained. With respect to projected syntheses of natural products of the types **1**–**5**, therefore, oxidative cyclisations of the type **14**→**15** do not appear to be attractive.

Experimental

^1H NMR spectra were recorded on JEOL PMX 60, GX 400 or EX 90 spectrometers, IR spectra were recorded on Perkin-Elmer 297 or 298 spectrometers and mass spectra on a Kratos MS 25 spectrometer. Microanalyses were determined by Mr. A. W. R. Saunders of the University of East Anglia. Column chromatography was performed using silica gel Merck 7734 (200–600 mesh), and analytical thin-layer chromatography was performed on aluminium-backed silica plates, Merck 5554. M.p.s were determined on a Kofler hot-stage apparatus. Acetonitrile was distilled from phosphorus pentoxide. Phenyliodine(III) bis(trifluoroacetate) (PIFA) was prepared by treatment of phenyliodine(III) diacetate[16] with trifluoroacetic acid.[17]

Oximes.—The following were prepared as described: 4-hydroxyphenylacetaldehyde oxime **10**,[9] 1-(4-hydroxyphenyl)-propan-2-one oxime **12a**,[4] methyl 4-hydroxyphenylpyruvate oxime **12g**,[4] methyl 3,5-dibromo-4-hydroxyphenylpyruvate oxime **12h**,[4] 4-hydroxybenzyl phenyl ketoxime **12i**.[19]

1-(3,5-*Dibromo*-4-*hydroxyphenyl*)*propan*-2-*one Oxime* **12b**. Bromine (1.33 g, 8.3 mmol) was added dropwise during 30 min to a stirred solution of 1-(4-hydroxyphenyl)propan-2-one[20] (0.65 g, 4.3 mmol) and anhydrous potassium acetate (2.5 g, 25 mmol) in acetic acid (15 g, 0.25 mol) at 0 °C. The mixture was stirred for a further 15 min, at which time TLC analysis

* We are grateful to Mr. M. Tinkl and Dr. A. K. Powell for the X-ray structural analysis, the details of which will be published elsewhere.

indicated complete consumption of starting material. Water (100 cm^3) was added, the resulting mixture was extracted with ether (3 × 75 cm^3), and the combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The pale yellow residue was purified by column chromatography (dichloromethane). This gave 0.55 g (42%) of 1-(3,5-*dibromo*-4-*hydroxyphenyl*)*propan*-2-*one* as colourless crystals, m.p. 97–98 °C (Found: C, 35.3; H, 2.55. Calc. for $C_9H_8Br_2O_2$: C, 35.09; H, 2.60%); $\nu_{max}(CH_2Cl_2)/cm^{-1}$ 3450 (OH), 1715 (C=O) and 1590 (arom C=C); δ_H(60 MHz; $CDCl_3$) 2.20 (3 H, s, Me), 3.60 (2 H, s, CH_2), 5.96 (1 H, s, OH) and 7.28 (2 H, s, arom); δ_C(90 MHz; $CDCl_3$) 29.41, 48.72, 109.91, 128.53, 132.85, 148.54 and 205.05; *m/z* 308 (19%, M^+ for ^{79}Br and ^{81}Br), 265 (6%, M^+ − MeCO) and 43 (100%, MeCO).

Sodium hydroxide solution (10%) was added to a mixture of hydroxylamine hydrochloride (0.5 g, 7.2 mmol) and 1-(3,5-dibromo-4-hydroxyphenyl)propan-2-one (0.2 g, 0.65 mmol) in water (4 cm^3) and ethanol (3 cm^3) until the pH was approximately 4. The mixture was heated gently for 1 h then cooled in an ice bath. The colourless crystalline solid was collected by filtration and dried. This gave 0.17 g (82%) of 1-(3,5-*dibromo*-4-*hydroxyphenyl*)*propan*-2-*one oxime*, m.p. 110–114 °C (Found: C, 33.7; H, 2.8; Br, 49.35; N, 4.15. Calc. for $C_9H_9Br_2NO_2$: C, 33.55; H, 2.79; Br, 49.59; N, 4.34%); ν_{max}(Nujol)/cm^{-1} 3250br (OH), 1660 (C=N) and 1570 (arom C=C); δ_H(60 MHz; CD_3OD) 1.76 (3 H, s, Me), 3.45 (2 H, s, CH_2), 4.96 (2 H, s, OH) and 7.28 (2 H, s, arom.); δ_C(90 MHz; [$^2H_6$]-acetone) 13.14, 40.80, 111.54, 133.23, 133.59, 150.29 and 155.81; *m/z* 323 (85%, M^+ for ^{79}Br and ^{81}Br), 265 (100%, M^+ − MeCNOH) and 58 (55%, MeCNOH).

1-(4-*Hydroxyphenyl*)*butan*-2-*one Oxime* **12c**. A solution of 1-(4-methoxyphenyl)butan-2-one[21] (3.48 g, 19.6 mmol) in dry benzene (10 cm^3) was added to a solution of aluminium chloride (12.28 g, 46 mmol) in dry benzene (80 cm^3) and the mixture was heated gently under reflux on a water bath for 8 h. During this time a red oil separated. The mixture was cooled and allowed to stand at room temp. for 10 h, after which it was quenched with conc. hydrochloric acid. The organic phase was separated and the aqueous phase extracted with ether (3 × 100 cm^3). The combined organic extracts were extracted with 2% aqueous sodium hydroxide solution (30 cm^3) and the basic extract was then acidified with acetic acid and extracted with ether (3 × 25 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered and the filtrate evaporated under reduced pressure. Column chromatography of the crude product thus obtained [light petroleum (b.p. 40–60 °C)–ether (1 : 1)] gave 2.76 g (86%) of 1-(4-*hydroxyphenyl*)*butan*-2-*one* as colourless crystals, m.p. 49–51 °C (lit.,[22] 49.5–50 °C).

Treatment of the ketone thus obtained with hydroxylamine hydrochloride as described for the oxime **12b** and recrystallisation of the crude product from water gave 1-(4-*hydroxyphenyl*)*butan*-2-*one oxime* **12c** in 86% yield as colourless crystals, m.p. 110–111 °C (Found: C, 67.35; H, 7.3; N, 7.75. Calc. for $C_{10}H_{13}NO_2$: C, 67.04; H, 7.26; N, 7.82%); ν_{max}(Nujol)/cm^{-1} 3450 (OH), 1660 (C=N) and 1620 (arom C=C); δ_H(60 MHz; $CDCl_3$) 1.85 (3 H, t, *J* 7, Me), 2.70 (2 H, q, *J* 7, CH_2), 3.75 (2 H, s, CH_2), 4.75 (1 H, s, OH) and 6.9–7.3 (4 H, AA'BB', *J* 8.4, arom.); δ_C(90 MHz; $CDCl_3$) 15.26, 27.68, 38.22, 115.28, 131.69, 133.66, 156.72 and 163.19.

1-(3,5-*Dibromo*-4-*hydroxyphenyl*)*butan*-2-*one Oxime* **12d**. Bromine (1.75 g, 10.9 mmol) was added dropwise to a stirred solution of 1-(4-hydroxyphenyl)butan-2-one (0.9 g, 5.5 mmol) and anhydrous potassium acetate (3.1 g, 32 mmol) in acetic acid (19.1 g, 0.32 mol) at 0 °C. The reaction mixture was stirred for 25 min then worked up as described for 1-(3,5-dibromo-4-hydroxyphenyl)propan-2-one. Column chromatography of the crude red product [light petroleum (b.p. 40–60 °C)–ether (1 : 1)] gave 0.92 g (52%) of 1-(3,5-*dibromo*-4-*hydroxyphenyl*)*butan*-2-*one* as yellow crystals, m.p. 77–79 °C (Found: C, 37.4; H, 3.2; Br 49.85. Calc. for $C_{10}H_{10}Br_2O_2$: C, 37.26; H, 3.10; Br, 49.69%); ν_{max}(Nujol)/cm^{-1} 3240 (OH) and 1685 (C=O); δ_H(60 MHz; $CDCl_3$) 1.25 (3 H, t, *J* 7, Me), 2.45 (2 H, q, *J* 7, CH_2), 3.80 (2 H, s, CH_2), 5.78 (1 H, s, OH) and 7.34 (2 H, s, arom.).

Treatment of the ketone thus obtained with hydroxylamine hydrochloride as described for the oxime **12b** and recrystallisation of the crude product from ethanol gave 1-(3,5-*dibromo*-4-*hydroxyphenyl*)*butan*-2-*one oxime* **12d** in 80% yield as colourless crystals, m.p. 157–160 °C (Found: C, 35.75; H, 3.3; Br, 47.55; N, 4.32. Calc. for $C_{10}H_{11}Br_2NO$: C, 35.60; H, 3.26; Br, 47.47; N, 4.15%); ν_{max}(Nujol)/cm^{-1} 3470 (OH) and 1590 (arom. C=C); δ_H(60 MHz; [$^2H_6$]acetone) 1.15 (3 H, t, *J* 7, Me), 2.18 (2 H, q, *J* 7, CH_2), 3.62 (2 H, s, CH_2), 4.61 (1 H, s, OH) and 7.32 (2 H, s, arom.); δ_C(90 MHz; [$^2H_6$]acetone) 19.22, 32.16, 41.08, 110.76, 131.38, 133.10, 149.96 and 159.44.

1-(4-*Hydroxyphenyl*)-3,3-*dimethylbutan*-2-*one Oxime* **12e**. A solution of 1-(4-methoxyphenyl)-3,3-dimethylbutan-2-one[23] (1.75 g, 8.5 mmol) in a mixture of 48% aqueous hydrobromic acid (9.6 cm^3, 85 mmol) and acetic acid (38 cm^3) was heated at reflux for 18 h then cooled, diluted with water (50 cm^3) and extracted with ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Chromatography of the crude product thus obtained [light petroleum (b.p. 40–60 °C)–ether (1 : 1)] gave 1.23 g (75%) of 1-(4-*hydroxyphenyl*)-3,3-*dimethylbutan*-2-*one* as colourless crystals, m.p. 127–129 °C (Found: C, 74.7; H, 8.55. Calc. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33); ν_{max}(Nujol)/cm^{-1} 3420 (OH), 3060 (arom. CH), 1698 (C=O) and 1610 (arom. C=C); δ_H(60 MHz; $CDCl_3$) 1.20 (9 H, s, CMe_3), 3.68 (2 H, s, CH_2), 6.24 (1 H, s, OH) and 6.84 (4 H, AA'BB', *J* 8.4, arom.); δ_C(90 MHz; $CDCl_3$) 26.37, 42.51, 44.57, 115.52, 126.14, 130.49, 154.72 and 215.19; *m/z* 192 (22%, M^+), 107 (89%, $M^+ - C_4H_9CO$), 85 (20%, C_4H_9CO), 77 (10%, C_6H_5) and 57 (100%, C_4H_9).

Treatment of the ketone thus obtained with hydroxylamine hydrochloride as described for the oxime **12b** gave 1-(4-*hydroxyphenyl*)-3,3-*dimethylbutan*-2-*one oxime* **12e** in 94% yield as colourless crystals, m.p. 159–160 °C (Found: C, 69.45; H, 8.45; N, 6.6. Calc. for $C_{12}H_{17}NO_2$: C, 69.57; H, 8.21; N, 6.76%); ν_{max}(Nujol)/cm^{-1} 3480 (OH), 1660 (C=N) and 1610 (arom. C=C); δ_H(60 MHz; CD_3OD) 1.80 (9 H, s, CMe_3), 3.68 (2 H, s, CH_2), 4.72 (2 H, s, OH) and 6.50–7.10 (4 H, AA'BB', *J* 8.4, arom.); *m/z* 207 (22%, M^+), 133 (100%, $ArCH_2CN$), 107 (95%, $M^+ - C_4H_9CNOH$) and 57 (87%, C_4H_9).

1-(3,5-*Dibromo*-4-*hydroxyphenyl*)-3,3-*dimethylbutan*-2-*one oxime* **12f**. Bromination of 1-(4-hydroxyphenyl)-3,3-dimethylbutan-2-one was carried out as described for 1-(4-hydroxyphenyl)propan-2-one (see **12b**). Purification of the red crude product by column chromatography [light petroleum (b.p. 40–60 °C)–ether (1 : 1)] gave 1-(3,5-*dibromo*-4-*hydroxyphenyl*)-3,3-*dimethylbutan*-2-*one* as a colourless solid, m.p. 95 °C (Found: C, 41.25; H, 4.0; Br, 45.7. Calc. for $C_{12}H_{14}Br_2O_2$: C, 41.17; H, 4.00; Br, 45.68%); ν_{max}(Nujol)/cm^{-1} 3227 (OH) and 1693 (C=O); δ_H(60 MHz; $CDCl_3$) 1.24 (9 H, s, CMe_3), 3.68 (2 H, s, CH_2), 5.88 (1 H, s, OH) and 7.24 (2 H, s, arom.); δ_C(90 MHz; $CDCl_3$) 26.31, 41.38, 44.57, 109.65, 129.38, 133.06, 148.23 and 211.98; *m/z* 85 (19%, C_4H_9CO) and 57 (100%, C_4H_9).

Treatment of the ketone thus obtained with hydroxylamine hydrochloride as described for the oxime **12b** gave 1-(3,5-*dibromo*-4-*hydroxyphenyl*)-3,3-*dimethylbutan*-2-*one oxime* **12f** in 89% yield as colourless crystals, m.p. 141 °C (Found: C, 39.7; H, 3.95; Br, 44.0; N, 3.6. Calc. for $C_{12}H_{15}Br_2NO_2$: C, 39.47; H, 4.11; Br, 43.80; N, 3.84%); ν_{max}(Nujol)/cm^{-1} 3485, 3263 (OH) and 1590 (arom. C=C); δ_H(60 MHz; CD_3OD) 1.04 (9 H, s, CMe_3), 3.62 (2 H, s, CH_2), 4.72 (2 H, s, OH) and 7.32 (2 H, s, arom.); δ_C(90 MHz; CD_3OD) 28.61, 29.50, 38.06, 111.10, 133.21, 149.49 and 163.85; *m/z* 291 (16%, $ArCH_2CN$), 265 ($M^+ - C_4H_9CNO$) and 57 (100%, C_4H_9).

3,5-Dibromo-4-hydroxybenzyl phenyl ketoxime **12j**. Bromination of 4-hydroxybenzyl phenyl ketone[19] was carried out as for 1-(4-hydroxyphenyl)propan-2-one (see **12b**). This gave 3,5-*dibromo-4-hydroxybenzyl phenyl ketone* in 52% yield as a colourless solid, m.p. 104–105 °C (Found: C, 45.7; H, 2.85; Br, 43.4. Calc. for $C_{14}H_{10}Br_2O_2$: C, 45.42; H, 2.70; Br, 43.21%); ν_{max}(Nujol)/cm^{-1} 3250 (OH) and 1685 (C=O); δ_H(60 MHz; $CDCl_3$) 3.62 (2 H, s, CH_2), 6.15 (1 H, s, OH) and 6.9–7.6 (7 H, m, arom.).

Treatment of the ketone thus obtained with hydroxylamine hydrochloride as described for the oxime **12b** gave 3,5-*dibromo-4-hydroxybenzyl phenyl ketoxime* **12j** in 89% yield as colourless crystals, m.p. 171–173 °C (Found: C, 43.7; H, 3.15; Br, 41.6; N, 3.7. Calc. for $C_{14}H_{11}Br_2NO_2$: C, 43.65; H, 2.85; Br, 41.52; N, 3.63%); ν_{max}(Nujol)/cm^{-1} 3450 (OH), 1660 (C=N) and 1570 (arom.); δ_H(60 MHz; CD_3OD) 3.52 (2 H, s, CH_2), 5.10 (2 H, s, OH) and 6.9–7.5 (7 H, m, arom.); δ_C(90 MHz; [$^2H_6$]acetone) 43.89, 111.58, 128.72, 129.56, 132.38, 133.63, 134.05, 150.26 and 158.81.

4-Bromophenyl 4-hydroxybenzyl ketoxime **12k**. A solution of 4-bromophenyl 4-methoxybenzyl ketone[24] (2.6 g, 8.5 mmol) in a mixture of 48% aqueous hydrobromic acid (10 cm^3, 85 mmol) and acetic acid (38 cm^3) was heated under reflux for 18 h, then cooled, diluted with water (50 cm^3) and the resulting mixture extracted with ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and the solvent evaporated under reduced pressure. Purification of the crude product thus obtained by column chromatography [light petroleum (b.p. 40–60 °C)–ethyl acetate (3:2)] gave 1.20 g (48%) of *4-bromophenyl 4-hydroxybenzyl ketone* as colourless crystals, m.p. 133–135 °C (Found: C, 58.05; H, 3.85; Br, 27.6. Calc. for $C_{14}H_{11}BrO_2$: C, 57.73; H, 3.78; Br, 27.49%); ν_{max}(Nujol)/cm^{-1} 3450 (OH), 1686 (C=O) and 1615 (arom. C=C); δ_H(60 MHz; $CDCl_3$) 3.72 (2 H, s, CH_2), 6.18 (1 H, s, OH) and 6.9–7.4 (8 H, m, arom.).

Treatment of the ketone thus obtained with hydroxylamine hydrochloride as described for the oxime **12b** gave *4-bromophenyl 4-hydroxybenzyl ketoxime* **12k** in 84% yield as colourless crystals, m.p. 158–160 °C (Found: C, 55.15; H, 4.0; Br, 26.3; N, 4.7. Calc. for $C_{14}H_{12}BrNO_2$: C, 54.90; H, 3.92; Br, 26.14; N, 4.57%); ν_{max}(Nujol)/cm^{-1} 3465 (OH), 1650 (C=N) and 1610 (arom. C=C); δ_H(60 MHz; CD_3OD) 3.62 (2 H, s, CH_2), 4.98 (1 H, s, OH) and 6.8–7.4 (8 H, m, arom.); δ_C(90 MHz; [$^2H_6$]-acetone) 43.86, 118.25, 124.11, 128.92, 131.08, 132.29, 132.83, 133.45, 156.13 and 161.54.

4-Bromophenyl 3,5-dibromo-4-hydroxybenzyl ketoxime **12l**. Bromination of 4-bromophenyl 4-hydroxybenzyl ketone was carried out as described for 1-(4-hydroxyphenyl)propan-2-one (see **12b**). Purification of the red crude product by column chromatography [light petroleum (b.p. 40–60 °C)–ether (3:1)] gave *4-bromophenyl 3,5-dibromo-4-hydroxybenzyl ketone* in 32% yield as light tan crystals, m.p. 103–105 °C (Found: C, 37.7; H, 2.2; Br, 53.75. Calc. for $C_{14}H_9Br_3O_2$: C, 37.44; H, 2.00; Br, 53.42); ν_{max}(Nujol)/cm^{-1} 3350 (OH) and 1680 (C=O); δ_H(60 MHz; $CDCl_3$) 3.62 (2 H, s, CH_2), 5.86 (1 H, s, OH), 7.28 (2 H, s, arom.) and 7.4–7.7 (4 H, AA'BB', *J* 8.4, arom.).

Treatment of the ketone thus obtained with hydroxylamine hydrochloride as described for the oxime **12b** gave *4-bromophenyl 3,5-dibromo-4-hydroxybenzyl ketoxime* **12l** as yellow crystals, m.p. 151–153 °C (Found: C, 36.4; H, 2.2; Br, 51.55; N, 2.95. Calc. for $C_{14}H_{10}Br_3NO_2$: C, 36.23; H, 2.15; Br, 51.69; N, 3.01%); ν_{max}(Nujol)/cm$^-$ 3480 (OH) and 1660 (C=N); δ_H(60 MHz; CD_3OD) 3.56 (2 H, s, CH_2), 5.72 (2 H, br, OH), 7.12 (2 H, s, arom.) and 7.3–7.7 (4 H, m, arom.); δ_C(90 MHz; CD_3OD) 41.05, 110.54, 123.66, 129.02, 129.89, 131.35, 133.22, 133.76, 151.14 and 155.81.

(2-Hydroxyphenyl)propan-2-one Oxime **14**. Repeated attempts to prepare (2-hydroxyphenyl)propan-2-one by peracetic acid oxidation of 1-(2-hydroxyphenyl)prop-1-ene[4,25] were unsuccessful, as were attempts to demethylate (2-methoxyphenyl)propan-2-one[26] with either HBr–acetic acid, BCl_3 or BBr_3. The title compound was therefore prepared by the general method of Sera *et al.*[18] Thus, a solution of 2-hydroxybenzaldehyde (1.66 g, 13.6 mmol), nitromethane (1.66 g, 22 mmol) and ammonium acetate (0.66 g, 8.6 mmol) in glacial acetic acid (6.7 cm^3) was heated at reflux for 2 h. The cooled reaction mixture was poured into ice–water (50 cm^3) and the resulting mixture extracted with ether (3 × 50 cm^3). The combined organic extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Purification of the crude black residue thus obtained by chromatography (dichloromethane) gave 0.73 g (30%) of *1-(2-hydroxyphenyl)-2-nitroprop-1-ene* as a yellow oil, b.p. 125 °C/0.4 mmHg (Found: C, 60.5; H, 5.25; N, 7.35. Calc. for $C_9H_9NO_3$: C, 60.34; H, 5.03; N, 7.82); ν_{max}(film)/cm^{-1} 3460 (OH), 1620 (arom. C=C) and 1500 (NO_2); δ_H(60 MHz; $CDCl_3$) 2.20 (3 H, s, Me, minor isomer) and 2.40 (3 H, s, Me, major isomer), 6.8–7.5 (4 H, m, arom.), 8.30 (1 H, s, =CH, minor isomer) and 8.40 (1 H, s, =CH, major isomer); *m/z* 179 (27%, M$^+$).

A mixture of the nitropropene (0.30 g, 1.7 mmol) and lead powder (0.70 g, 3.4 mmol) in acetic acid (0.83 cm^3) and dimethylformamide (12.5 cm^3) was stirred at room temp. for 7 h, then poured into ice–water (100 cm^3) and the resulting mixture extracted with ether (2 × 100 cm^3). The combined organic extracts were washed with aqueous sodium chloride (75 cm^3), dried ($MgSO_4$), filtered, and the filtrate evaporated under reduced pressure. Purification of the crude product thus obtained by chromatography [dichloromethane–ether (9:1)] gave 0.097 g (35%) of *1-(2-hydroxyphenyl)propan-2-one oxime* **14** as a mixture of *syn* and *anti* isomers, m.p. 78–81 °C (lit.,[4] 80–81 °C).

General Procedure for Oxidative Cyclisation of the Oximes **10**, **12a–l** *and* **14**.—A solution of the oxime (3 mmol) in acetonitrile (25 cm^3) was heated gently at reflux under a nitrogen atmosphere and PIFA (1.42 g, 3.3 mmol) was added gradually. TLC analysis indicated complete consumption of starting material after 30–60 min. The cooled reaction mixture was quenched with an excess of saturated aqueous sodium carbonate and extracted with dichloromethane (3 × 75 cm^3). The combined organic extracts were dried ($MgSO_4$), filtered, and the filtrate evaporated under reduced pressure. This gave a black residue from which the pure product was obtained by chromatography (see below). For the oximes **12a–l** the reaction can be carried out equally conveniently either in acetonitrile at 0 °C or in ethanol at reflux temperature for 30–60 min. Use of nitromethane as solvent gave poor yields (*ca.* 25%) and running the reactions at low temperatures (down to −50 °C) did not result in any noticeable increase in yield. In most cases, addition of all of the PIFA in one batch did not affect the yield, but portionwise addition was necessary with oxime **10**.

1-Oxa-2-azaspiro[4.5]*deca-2,6,9-trien-8-one* **11**. Obtained as a pure yellow oil in 20% yield after chromatography [light petroleum (b.p. 40–60 °C)–ethyl acetate (1 : 1)] and Kugelrohr distillation, b.p. 92–94 °C–0.4 mmHg (lit.,[4] 113 °C/1 mmHg). The IR and NMR data were as reported.[4]

3-Methyl-1-oxa-2-azaspiro[4.5]*deca-2,6,9-trien-8-one* **13a**. Obtained in 63% yield as colourless plates after chromatography [light petroleum (b.p. 40–60 °C)–ethyl acetate (1 : 1)], m.p. 70–71 °C (lit.,[4] 70.5–73 °C). The IR and NMR spectroscopic data were as reported.

7,9-Dibromo-3-methyl-1-oxa-2-azaspiro[4.5]*deca-2,6,9-trien-8-one* **13b**. Obtained in 58% yield as colourless crystals after chromatography [light petroleum (b.p. 40–60 °C)–ether (1 : 4)], m.p. 205–206 °C (decomp.) (Found: C, 33.7; H, 2.35; Br, 49.5; N, 4.1. Calc. for $C_9H_7Br_2NO_2$: C, 33.67; H, 2.18; Br, 49.81;

N, 4.36%): ν_{max}(Nujol)/cm^{-1} 1681 (C=O) and 1601 (C=C); δ_H(60 MHz; $CDCl_3$) 2.08 (3 H, s, Me), 3.20 (2 H, s, CH_2), and 7.32 (2 H, s, CH=); δ_C(90 MHz; $CDCl_3$) 13.07, 47.92, 83.00, 122.83, 146.10, 155.59 and 160.00; *m/z* 280 (57%, M^+ − MeCN) and 264 (100%, M^+ − MeCNO).

3-*Ethyl*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13c**. Obtained in 68% yield as colourless crystals after chromatography [light petroleum (b.p. 40–60 °C)–ether (1:3)], m.p. 78–81 °C (Found: C, 67.85; H, 6.25; N, 7.95. Calc. for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21; N, 7.90%); ν_{max}(Nujol)/cm^{-1} 1675 (C=O) and 1610 (C=C); δ_H(60 MHz; $CDCl_3$) 1.45 (3 H, t, *J* 7, Me), 2.15 (2 H, q, *J* 7, CH_2), 3.20 (2 H, s, CH_2), 6.35 (2 H, d, *J* 8.4, CH=) and 7.15 (2 H, d, *J* 8.4, CH=); δ_C(90 MHz; $CDCl_3$) 18.72, 33.58, 44.51, 82.81, 128.63, 144.91, 162.24 and 184.66.

7,9-*Dibromo*-3-*ethyl*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13d**. Obtained in 52% yield as colourless crystals after chromatography [dichloromethane–ether (1:3)], m.p. 199–202 °C (Found: C, 36.1; H, 2.7; Br, 47.9; N, 4.3. Calc. for $C_{10}H_9Br_2NO_2$: C, 35.84; H, 2.68; Br, 47.78; N, 4.18%); ν_{max}(Nujol)/cm^{-1} 1680 (C=O) and 1592 (C=C); δ_H(60 MHz; $CDCl_3$) 1.38 (3 H, t, *J* 7, Me), 2.23 (2 H, q, *J* 7, CH_2), 3.52 (2 H, s, CH_2) and 7.34 (2 H, s, CH=); δ_C(90 MHz; $CDCl_3$) 18.04, 36.41, 44.20, 84.91, 121.68, 146.10, 158.98 and 165.23.

3-tert-*Butyl*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13e**. Obtained in 93% yield as colourless crystals after chromatography [light petroleum (b.p. 40–60 °C)–ether (1:1)], m.p. 90–93 °C (Found: 70.2; H, 7.6; N, 6.7. Calc. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.32; N, 6.83%); ν_{max}(Nujol)/cm^{-1} 1670 (C=O) and 1610 (C=C); δ_H(60 MHz; $CDCl_3$) 1.28 (9 H, s, CMe_3), 3.12 (2 H, s, CH_2), 6.20 (2 H, d *J* 9.6, CH=) and 6.90 (2 H, d *J* 9.6, CH=); δ_C(90 MHz; $CDCl_3$) 28.03, 33.53, 44.51, 78.80, 128.63, 145.69, 166.24 and 184.72; *m/z* 205 (10%, M^+), 148 (36%, M^+ − C_4H_9) and 57 (100, C_4H_9).

7,9-*Dibromo*-3-tert-*butyl*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13f**. Obtained in 89% yield as colourless crystals after chromatography [light petroleum (b.p. 40–60 °C)–dichloromethane (2:3)], m.p. 191–195 °C (Found: C, 39.7; H, 3.5; Br, 44.1; N, 3.75. Calc. for $C_{12}H_{13}Br_2NO_2$: C, 39.69; H, 3.58; Br, 44.04, N, 3.86%); ν_{max}(Nujol)/cm^{-1} 1683 (C=O) and 1592 (C=C); δ_H(60 MHz; $CDCl_3$) 1.28 [9 H, s, $C(Me_3)$], 3.24 (2 H, s, CH_2) and 7.32 (2 H, s, CH=); δ_C(90 MHz; $CDCl_3$) 28.03, 33.67, 43.96, 83.31, 122.68, 146.05, 166.43 and 171.58; *m/z* 306 (12%, M^+ − C_4H_9) and 57 (89%, C_4H_9).

Methyl 8-*oxo*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*triene*-3-*carboxylate* **13g**. Obtained in 65% yield as colourless plates after chromatography [light petroleum (b.p. 40–60 °C)–ether (3:2)] m.p. 81–83 °C (lit.,[4] 82–83 °C). The IR and NMR data were as reported.[4]

Methyl 7,9-*dibromo*-8-*oxo*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*triene*-3-*carboxylate* **13h**. Obtained in 58% yield as colourless plates after chromatography [light petroleum (b.p. 40–60 °C)–ethyl acetate (1:1)], m.p. 198–199 °C (lit.,[4] 199–200 °C). The IR and NMR data were as reported.[4]

3-*Phenyl*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13i**. Obtained in 86% yield as colourless crystals after chromatography [light petroleum (b.p. 40–60 °C)–ether (1:1)], m.p. 71–73 °C (Found: C, 74.8; H, 5.1; N, 6.3. Calc. for $C_{14}H_{11}NO_2$: C, 74.66; H, 4.88; N, 6.22%); ν_{max}(Nujol)/cm^{-1} 1670 (C=O) and 1620 (C=C); δ_H (60 MHz; [$^2H_6$] acetone) 3.54 (2 H, s, CH_2), 6.30 (2 H, d, *J* 7.2, CH=), 6.90 (2 H, d, *J* 7.2, CH=) and 7.4–7.6 (5 H, m, arom.); δ_C(90 MHz; [$^2H_6$]acetone) 43.86, 78.80, 128.76, 128.93, 129.88, 132.08, 134.21, 145.21, 145.69, 166.24 and 184.72.

7,9-*Dibromo*-3-*phenyl*-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13j**. Obtained in 78% yield as colourless crystals after chromatography [dichloromethane–ether (1:3)], m.p. 209–211 °C (Found: C, 44.15; H, 2.4; Br, 41.95; N, 3.7. Calc. for $C_{14}H_9Br_2NO_2$: C, 43.86; H, 2.35; Br, 41.77; N, 3.65); ν_{max}(Nujol)/cm^{-1} 1680 (C=O) and 1600 (C=C); δ_H(60 MHz; [$^2H_6$]acetone) 3.42 (2 H, s, CH_2) and 6.7–7.4 (7 H, m, arom. and CH=); δ_C(90 MHz; [$^2H_6$]acetone) 48.11, 83.72, 123.61, 128.87, 129.96, 133.41, 133.54, 146.16, 155.60 and 161.24.

3-(4-*Bromophenyl*)-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13k**. Obtained in 82% yield as colourless crystals after chromatography [dichloromethane–ether (1:1)], m.p. 96–98 °C (Found: C, 55.25; H, 3.3; Br, 26.3; N, 4.6. Calc. for $C_{14}H_{12}BrNO_2$: C, 55.42; H, 3.32; Br, 26.48; N, 4.65%); ν_{max}(Nujol)/cm^{-1} 1675 (C=O) and 1615 (C=C); δ_H(60 MHz; $CDCl_3$) 3.16 (2 H, s, CH_2), 6.20 (2 H, d, *J* 7.2, CH=), 6.80 (2 H, d, *J* 7.2 CH=) and 7.40–7.70 (4 H, AA'BB', *J* 8.4, arom.); δ_C(90 MHz; $CDCl_3$) 44.21, 78.80, 125.42, 128.11, 129.33, 129.46, 133.10, 145.69, 167.81 and 185.08.

7,9-*Dibromo*-3-(4-*bromophenyl*)-1-*oxa*-2-*azaspiro*[4.5]*deca*-2,6,9-*trien*-8-*one* **13l**. Obtained in 77% yield as yellow crystals after chromatography [light petroleum (b.p. 40–60 °C)–ether (1:3)], m.p. 216–217 °C (Found: C, 36.4; H, 1.7; Br, 52.15; N, 2.85. Calc. $C_{14}H_8Br_3NO_2$: C, 36.38; H, 1.73; Br, 51.91; N, 3.03%); ν_{max}(Nujol)/cm^{-1} 1680 (C=O) and 1600 (C=C); δ_H(60 MHz; $CDCl_3$) 3.42 (2 H, s, CH_2) and 7.2–7.8 (6 H, m, arom. and CH=); δ_C(90 MHz; [$^2H_6$]acetone) 46.30, 84.15, 122.68, 123.84, 126.19, 129.34, 133.96, 146.81, 165.92 and 171.31.

Oxidative Cyclisation of 1-(2-*Hydroxyphenyl*)*propan*-2-*one Oxime* **14**; *Formation of the Dimer* **16**.—Purification of the crude product by chromatography [dichloromethane–ethyl acetate (1:1)] gave **16** in 45% yield as colourless crystals, m.p. 206–208 °C. A satisfactory microanalysis could not be obtained, as the product crystallised wtih one molecular equivalent of dichloromethane in the crystal lattice; ν_{max}(Nujol)/cm^{-1} 1730 and 1700 (C=O); δ_H(400 MHz; $CDCl_3$) 1.96 (3 H, s, Me), 1.98 (3 H, s, Me), 2.65 (1 H, d, *J* 17.14, CH_2), 2.97 (1 H, d, *J* 17.4, CH_2), 3.15 (2 H, m, CH_2), 3.35 (1 H, m, CH), 3.40 (2 H, m, 2 × CH), 3.48 (1 H, m, CH), 6.04 (1 H, m, CH=), 6.20 (1 H, d, *J* 10.2, =CH-CO) and 6.51 (2H, m, CH=); δ_C(DEPT) (90 MHz; $CDCl_3$) 12.7 (Me), 12.8 (Me), 37.6 (CH), 42.6 (CH), 43.8 (CH), 49.6 (CH_2), 50.7 (CH_2), 52.5 (CH), 128.7 (CH=), 130.1 (CH=), 135.8 (CH=) and 146.1 (CH=); *m/z* 326 (4.8%, M^+), 104 (100%, C_7H_6O) and 57 (73%, MeCNO).

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