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Original article

Synthesis and antispasmodic activity of nature identical substituted indanes and analogues

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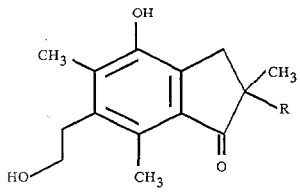
Summary — The synthesis of a series of substituted indanes which provide routes to nature-identical compounds and their analogues is reported. The smooth muscle relaxant activity of a series of substituted indanes and indanones together with their analogues has been measured. A compound with significant smooth muscle relaxant activity has been identified.

Résumé — Synthèse et activité antispasmodique d'indanes substitués et d'analogues de composés naturels. La synthèse d'une série de dérivés de 2,3-dihydro-1H-indènes et de composés analogues qui permettent d'obtenir des composés identiques à ceux qui existent dans la nature a été réalisée. L'activité relaxante d'une série de 2,3-dihydro-1H-indènes, et de leurs analogues vis-à-vis des muscles lisses a été déterminée. Un composé d'activité relaxante importante a été identifié.

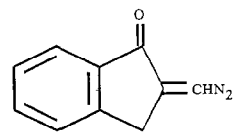
indanes / indanones / pterosins / smooth muscle relaxant activity

Introduction

A series of naturally occurring sesquiterpene indanes, the pterosins, have been identified in the plant kingdom [1–3]. Two compounds in this series onitin **1** and onitinsin **2** are reported to exhibit smooth muscle relaxant activity [4, 5]. Although many synthetic indanone derivatives show therapeutic effects *eg* the analgesic drindene **3** [6] and the mediator release inhibitor nivimedone **4** [7], the pharmacological activity of a range of natural indanes, indanones and their derivatives has not been reported. This is due mainly to the scarcity of the natural products, and has prompted us to report on the synthesis and smooth muscle relaxant activity of naturally occurring substituted indanes, indanones and their analogues.



(1) R = CH_3
(2) R = CH_2OH



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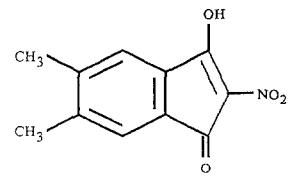

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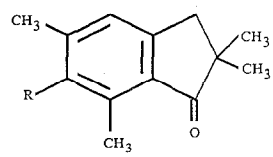

(5) a; R = Halogen
b; R = Alkyl

Chemistry

Compounds with the basic indanone skeleton **5** were identified as key intermediates in the total synthesis of this series of natural products. Two routes to substituted indanones of this type were investigated using a common starting material, bromo-*m*-xylene **6**. The first route (scheme 1) involved elaboration of the indanone skeleton prior to substitution of the aromatic halogen. This scheme was only suitable for the synthesis of the naturally occurring indanes.

In this route (scheme 1) Friedel-Crafts acylation of bromo-*m*-xylene **6** with *ß*-chloropropionyl chloride led to a 1:1 mixture of structural isomers **7** and **8** which were easily separated by preparative TLC. Acid catalysed cyclisation of isomer **7** gave **9** which was methylated in quantitative yield to **10**. Replacement of the bromine atom in **10** by lithiation followed by reaction with ethylene oxide proved unsuccessful using

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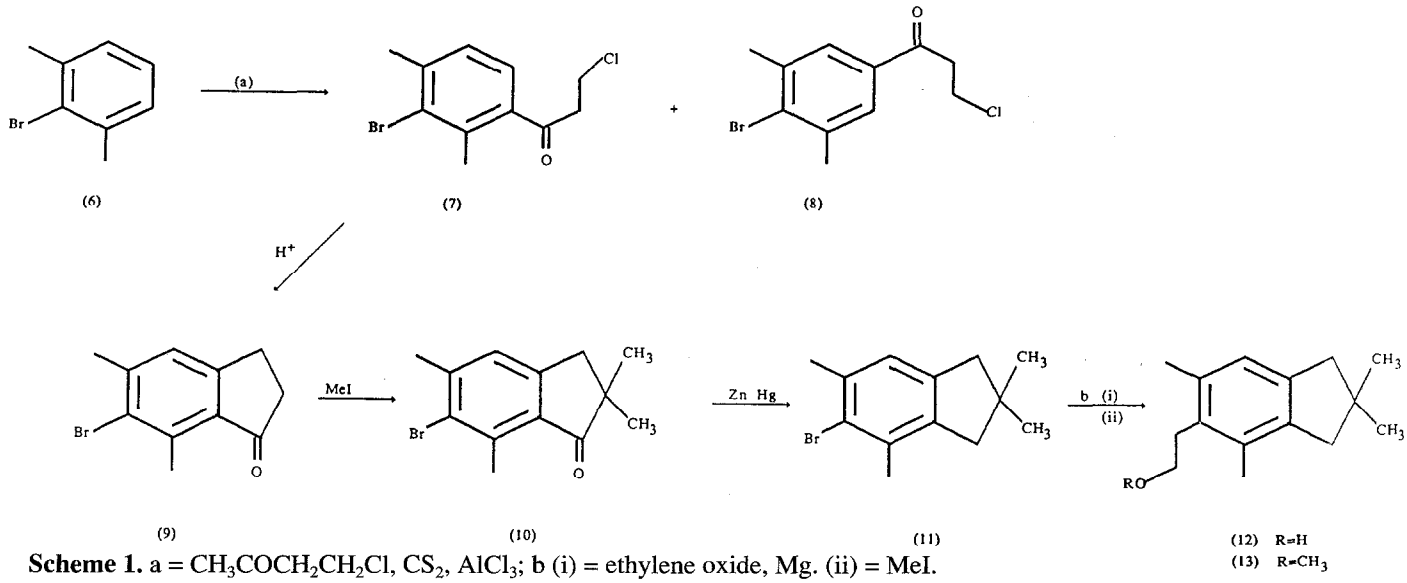
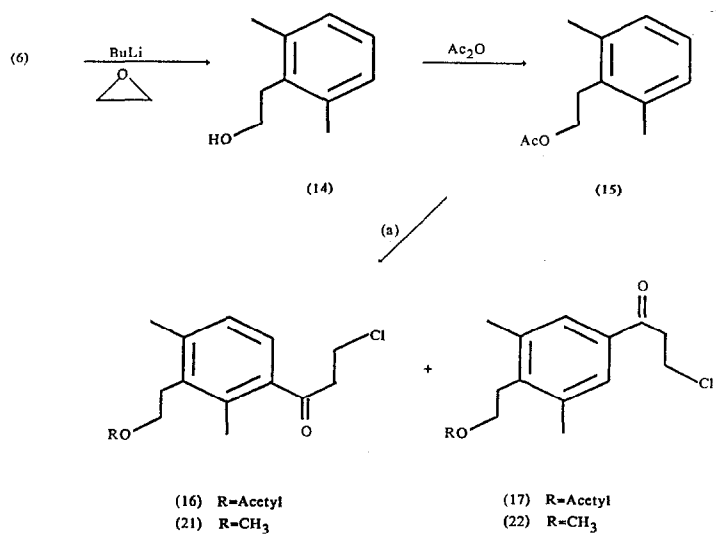


Scheme 1. a = $CH_3COCH_2CH_2Cl$, CS_2, $AlCl_3$; b (i) = ethylene oxide, Mg. (ii) = MeI.

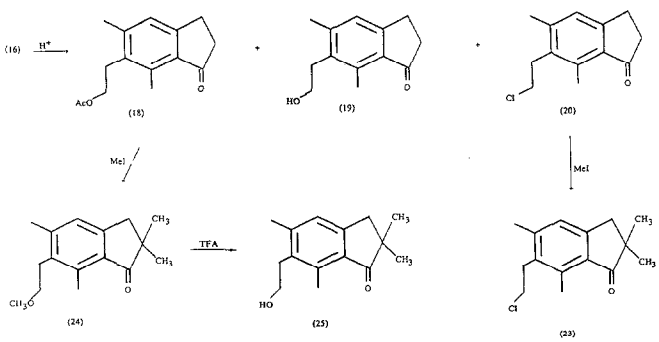
a range of bases (*n*-BuLi, LDA, Ph.Li). However, conversion of **10** to its indane analogue **11** by Clemensen reduction, followed by formation of the grignard reagent and reaction with ethylene oxide proved to be a successful route to the synthesis of the indane series of natural products (*eg* **12** and **13**) and their analogues.

The second route (scheme 2), previously reported by McMorris [8], in which the bromine atom of **6** is replaced in the initial reaction step, was found to be suitable for the synthesis of the indanone related natural products. In this route the hydroxyethyl group was introduced at C-5 of bromo-*m*-xylene **6** by reaction with *n*-butyl lithium and ethylene oxide yielding **14** which was protected as the previously unreported acetate ester **15**. Friedel-Crafts acylation of **15** with *β* chloropropionyl chloride results in a 1:1 mixture of the desired product **16** and its structural isomer **17**.



Scheme 2. a = $CH_3COCH_2CH_2Cl$, CS_2, $AlCl_3$.

Sulphuric acid catalysed cyclization of **16** (scheme 3) led to the isolation of several compounds of which the targeted products **18** and **19** were readily identified. In most cases the isomeric mixture **16** and **17** was cyclized without separation as the products were more easily separated than the acyclic precursors. The use of a higher cyclization temperature gave increased yields of a 3rd compound with molecular formula $C_{13}H_{15}ClO$ (by high resolution mass spectrometry (M^+ 222.0811) and elemental analysis). The IR spectrum exhibited a carbonyl stretch at 1715 cm^{-1} consistent with a cyclopentanone derivative. The ^1H NMR spectrum (270 MHz) had signals at 3.32 and 3.45 ppm corresponding to the methylene protons of a C_2 side chain together with a signal at 7.13 ppm integrating for 1 aromatic proton. These data supported the structure of an unusual rearrangement product **20**, similar to that proposed by McMorris [8] for a compound recovered from the acid catalysed cyclisation of an isomeric mixture of the analogues **21** and **22**. The structure of the unexpected product **20** was confirmed by X-ray crystal analysis of its gem dimethyl derivative **23**, which proved to be identical to the natural product pterosin H [1]. Figure 1 shows the molecular structure of **23** with the hydrogen atoms omitted, together with the numbering system. This is the first report of an X-ray structure for this series of natural products and unambiguously establishes the substitution pattern for these compounds.



Scheme 3.

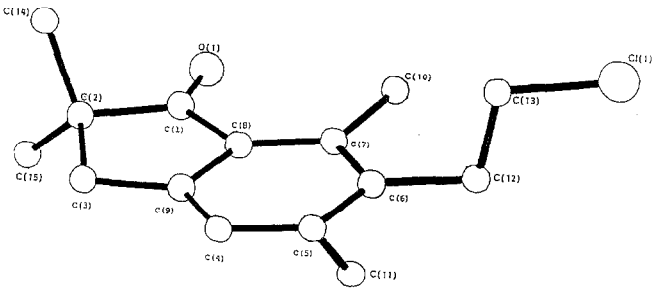


Fig 1. X-ray crystal structure of **23**.

The acetate ester **18** (scheme 3) was produced in moderate yield from the low temperature cyclization of **16** and was used directly for the synthesis of the nature identical substituted indanones **24** and **25**. Base catalysed methylation of **18** yielded pterosin I **24** [1, 3] which was converted to pterosin Z **25** by demethylation with trifluoroacetic acid. Spectroscopic data for the pterosins and their analogues was consistent with assigned structures.

Pharmacological results and discussion

The smooth muscle relaxant activity of the synthetic and nature identical indanes, indanones and their precursors was analysed. Addition of 25 mM $CaCl_2$ to isolated guinea pig ileum bathed in high potassium (45 mM) calcium-free Kreb's solution caused a sustained contracture which could be maintained for at least 40 min. A solvent control, consisting of 0.3 ml of a 10% ethanol solution, had no significant effect on the contracture ($P > 0.05$, $n = 6$). Calcium contractures were challenged by all the synthesised compounds at a concentration of 3×10^{-6} M ($n = 6$). The most potent activity was exhibited by **12** (76.8 ± 11.5%, $n = 6$) with other active compounds (**9**, **11**, **18**, **20**, **23**) showing inhibition values ranging between 5 and 16%. The results of these experiments are summarised in table I.

Compound **12** was shown to inhibit the calcium contracture in a dose dependent manner (fig 2) with threshold inhibition occurring at 3×10^{-8} M and having an ED_{50} value of $2.9 \pm 1.6 \times 10^{-6}$ ($n = 6$)-. The smooth muscle relaxant activity for the synthetic **12** was approximately 2 orders of magnitude greater than that previously reported for onitin (ED_{50} 1×10^{-4} M) **1** and onitinsin (ED_{50} 2×10^{-3} M) **2** [5]. The structure of **12** differs from that of the known relaxants onitin **1** and onitinsin **2** by the absence of an aromatic hydroxyl at C-4 and a carbonyl function at C-1. The correlation between C-1 and C-4 substitution and structure activity is currently under investigation.

Table I. Smooth muscle relaxant activity was exhibited by the following products on isolated guinea pig ileum.

Compound	*% Inhibition at 3 x10^{-6} M*
9	5.2 ± 3.0
11	12.5 ± 3.8
12	76.8 ± 11.5
18	13.7 ± 4.6
20	11.2 ± 0.8
23	15.7 ± 1.7

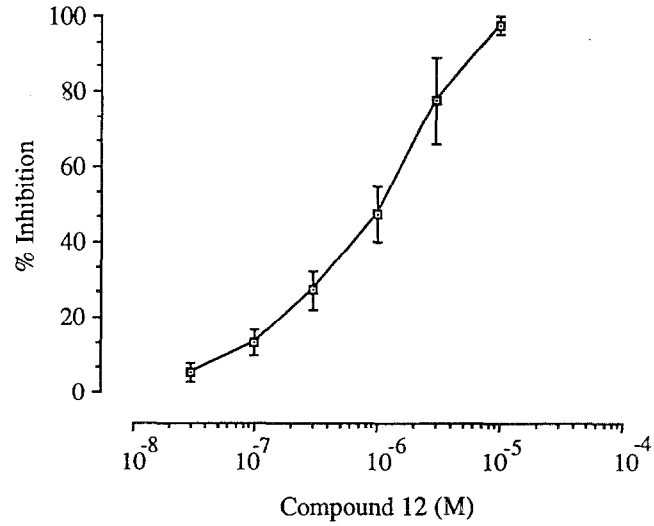


Fig 2. Inhibition of calcium contractures of guinea pig ileum by compound **12**. Values are expressed as a mean ± SEM $n = 6$.

Conclusion

The results of our experiments demonstrate that the synthetic routes investigated are suitable for the

synthesis of a range of nature-identical indanes and indanones and their analogues. In particular, one natural pterosin **12** has been synthesised which exhibits significant smooth-muscle relaxant activity. The activity for this compound is almost 2 orders of magnitude greater than that reported for related compounds.

Experimental protocols

Synthesis

Melting points were determined on a Me-Opta hot stage and are uncorrected. Infra red spectra were recorded with a Perkin-Elmer 157 spectrophotometer. Ultra violet spectra were recorded on a Pye-Unicam Sp-8-100 spectrophotometer. Mass spectra were determined at 70 eV on an AE1 MS 30 instrument. ^1H NMR spectra were recorded on a Perkin-Elmer R-12B 60 MHz and on a JOEL 270 MHz instrument. ^{13}C NMR spectra were recorded at 90.15 MHz. Deuteriochloroform was used as a solvent with $SiMe_4$ as internal standard. TLC's were run on commercially pre-coated plates (Merck, Kieselgel $60F_{254}$). Merck Kieselgel PF_{254} and PF_{366} was used for preparative TLC and Merck Kieselgel 60(9385) was used for column chromatography.

Synthesis of 3-(3'-Bromo-2',4'-dimethylphenyl)-1-chloro-3-oxopropane 7 and 3-(4'-bromo-3',5'-dimethylphenyl)-1-chloro-3-oxo-propane 8

Bromo-*m*-xylene **6** (10 g, 54 mmol) in CS_2 (7 ml) was added dropwise over 20 min to a stirred suspension of *β*-chloropropionylchloride (7.48 g, 59 mmol) and $AlCl_3$ (10 g, 75 mmol) in CS_2 (50 ml) at O°C. The reaction mixture was stirred at 0°C for a further 3 h. The reaction was monitored by TLC (pet ether:ethyl acetate 8:2), and on completion the CS_2 layer was decanted and the tarry residue added carefully to iced water. The aqueous solution was extracted with ethyl acetate (200 ml), washed with water (2 x 50 ml), dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography on silica gel (eluant:pet ether:ethyl acetate 8:2) to yield a mixture of **7** and **8** (10.4 g, 70%) which were separated by prep TLC (developer; pet ether:ethyl acetate 8:2). The least polar product was identified as **8**; mp = 101-102°C. (Found M^+ 275.9566, $C_{11}H_{12}BrClO$ requires M^+ 275.9828). ν_{max} (KBr) 1675, 1590, 1350, 1175, 660 cm^{-1}; λ_{max} (MeOH) 264 nm; δ_H ($CDCl_3$) 2.5 (6H, s, 2 x CH_3), 3.5 (2H, t, CH_2), 3.9 (2H, t, CH_2), 7.67 (2H, s, 2 x Ar*H*); δ_C ($CDCl_3$) 24.5 (q), 38.8 (t), 42.2 (t), 127.7 (d), 134.4 (s), 134.6 (s), 139.5 (s), 196.6 (s); m/z 275 (M^+, 40), 212(94), 210(100), 184(18), 104(56), 77(28).

The most polar compound identified as **7** was isolated as an oil (Found M^+ 275.9686, $C_{11}H_{12}BrClO$ requires M^+ 257.9828). ν_{max} (film) 1680, 1595 cm^{-1}; λ_{max} (MeOH) 264 nm; δ_H ($CDCl_3$) 2.4 (6H, s, 2 x CH_3), 3.5 (2H, t, CH_2), 3.9 (2H, t, CH_2), 7.25 (1H, d, J = 8.2 Hz, Ar*H*), 7.6 (1H, d, J = 8.2 Hz, Ar*H*); δ_C ($CDCl_3$) 24.5 (q), 38.8 (t), 42.2 (t), 127.7 (d), 134.4 (s), 134.6 (s), 139.5 (s), 196.6 (s); m/z 275 (M^+, 40).

6-Bromo-5,7-dimethylindan-1-one 9

A solution of **7** (2.0 g, 7.25 mmol) in conc.sulphuric acid (35 ml) was heated on a water bath at 90°C (Insufficient dilution or temperatures exceeding 90°C gave increased charring and decreased yield). After 1 h the reaction mixture was poured onto iced water (200 ml) and the aqueous solution extracted with ethyl acetate (200 ml). The organic layer was washed with water (200 ml), dried (Na_2SO_4) and evaporated. The residue (1.69 g) was purified by column chromatography on silica gel (eluant; pet ether-ethyl acetate 9:1) to yield the titled compound **9** (1.03 g, 60%), mp = 59°C (from ethanol). (Found M^+ 237.9951, $C_{11}H_{11}BrO$ requires M^+237.9994). ν_{max} (KBr) 2920, 1705, 1595, 1440, 1315 cm^{-1}; λ_{max} (MeOH) 211 nm; δ_H ($CDCl_3$) 2.45 (3H, s, CH_3), 2.65 (3H, s, CH_3), 2.9 (2H, t, CH_2), 3.04 (2H, t, CH_2), 7.26 (1H, s, Ar*H*); δ_C ($CDCl_3$) 19.46 (t), 24.25 (q), 36.85 (t), 122.65 (d), 133.6 (s), 136.7 (s), 138.54 (s), 152.83 (s), 205 (s); m/z 237 (M^+, 100), 212(19), 210(18), 159(22), 131(41), 128(15).

6-Bromo-2,2,5,7-tetramethyl-indan-1-one 10

A solution of **9** (700 mg, 2.94 mmol) dissolved in benzene (10 ml) was methylated as for **20** to yield a residue (0.815 g) which was purified by column chromatography (eluant: pet.ether:ethyl acetate 9:1) giving the titled compound **10** (383 mg, 49%); mp = 69-71°C (Found M^+ 266.0278; $C_{13}H_{15}BrO$ requires M^+ 266.0307). ν_{max} (KBr) 2950, 1715, 1315, 1055 cm^{-1}; λ_{max} (MeOH) 263 nm; δ_H ($CDCl_3$) 1.22 (6H, s, 2 x CH_3), 2.4 (3H, s, ArCH_3), 2.46 (3H, s, ArCH_3), 2.9 (2H, s, CH_2), 7.48 (1H, s, Ar*H*); δ_C ($CDCl_3$) 18.8, 23.7, 42.04 (q), 45.34 (s), 122.46 (d), 133.2 (s), 134 (s), 135 (s), 137 (s), 149 (s), 207 (s). m/z 266 (M^+, 79), 253(100), 188(4), 172(17), 171(18), 144(18), 129(25), 115(20).

6-Bromo-2,2,5,7-tetramethylindan 11

A solution of **10** (400 mg, 1.49 mmol) in equal volumes of ethanol and conc HCl (200 ml) was refluxed with an excess of Zn-Hg amalgam. Work-up (as for **13**) yielded the titled compound **11** as an oil (280 mg, 74%) which was purified by column chromatography on silica gel (eluant; pet.ether:ethyl acetate, 4:1) (Found M^+ 253.0513, $C_{13}H_{17}Br$ requires 253.0592). ν_{max} (film) 2980, 1455 cm^{-1}; λ_{max} (EtOH) 271 nm; δ_H ($CDCl_3$) 1.2 (6H, s, 2 x CH_3), 2.35 (3H, s, ArCH_3), 2.40 (3H, s, ArCH_3), 2.75 (4H, d, 2 x CH_2), 6.95 (1H, s, Ar*H*); m/z 253 (M^+, 23), 252(100), 237(10), 173(78), 158(76), 143(24), 128(18).

2(2',6'-Dimethylphenyl)-ethanol 14

A solution of bromo-*m*-xylene **6** (5 g, 27 mmol) in dry THF (6 ml) was added dropwise, under N_2 to a stirred solution of *n*-BuLi (20 ml, 1.6 M in hexane, 31.9 mmol) in dry THF (30 ml) at –78°C forming a white precipitate. The reaction mixture was stirred at this temperature for 30 min. Ethylene oxide (0.50 g, 11.4 mmol) was introduced under a dry-ice condenser and the reaction was stirred at –78°C for 1 h. The reaction temperature was raised to room temperature over 90 min and stirring was maintained for a further 3 h. The reaction mixture was poured over ice-water and the organic layer was separated, washed (H_2O, 100 ml), dried (Na_2SO_4) and evaporated to yield a crude residue which was purified by column chromatography on silica gel (eluant: pet ether - ethyl acetate 8:2 to 7:3) to yield the title compound **14**, (3.01 g, 74.5%) as white crystals; mp = 59°C (from hexane). Found: C, 80.61; H, 9.83·$C_{10}H_{14}O$ requires C, 80.00; H, 9.80%.

2,3-Dihydro-6-[2-hydroxyethyl]-2,2,5,7-tetramethyl-1H-inden 12 (Pterosin Z)

Route 1. A solution of **11** (200 mg, 0.79 mmol) in dry diethyl ether (5 ml) was added simultaneously with dibromoethane 2 ml) in dry diethyl ether (3 ml), under a nitrogen atmosphere, onto the surface of freshly ground magnesium turnings (24 mg). The reaction flask was warmed until all the magnesium was consumed. The grignard reagent **25** was cooled to –78°C and ethylene oxide (34 mg, 0.77 mmol) was introduced under a

dry ice condenser. The reaction mixture was stirred at –78°C for 1 h and at 0°C for 1 h, filtered and added to diethyl ether : water (1:1, 20 ml). The ether layer was washed (H_2O, 10 ml), dried (Na_2SO_4) and evaporated under vacuum to give a residue which was purified by column chromatography (eluant; pet ether-ethyl acetate 7:3) to yield **12** (43 mg, 25%) as an oil. Found M^+ 218.1684, $C_{15}H_{22}O$ requires 218.1671. IR, UV and NMR spectra were identical to the compound obtained from **13**.

Route 2. A solution of **13** (35 mg, 0.15 mmol) in equal volumes of TFA and HCl (10 ml) was heated to 80°C under reflux for 2 h. The reaction mixture was poured over NaOH (10%) and the resulting mixture was extracted with ethyl acetate. The organic layer was washed (H_2O), dried (Na_2SO_4) and evaporated to give a crude residue, which on purification by column chromatography on silica gel (eluant: CH_2Cl_2) gave **12** as a colourless oil (10 mg, 31%). Found M^+ 218.1684, $C_{15}H_{22}O$ requires 218.1671.

*2(2',6'-Dimethylphenyl)-ethanoacetate **15***

A solution of **14** (3.017 g, 2.01 mmol) in acetic anhydride (20 ml) and pyridine (1 ml) was refluxed for 4 h. The reaction mixture was poured on ice (50g)-HCl (20 ml, 10%) and was extracted into ethyl acetate (100 ml) which was dried (Na_2SO_4) and evaporated under vacuum to yield a crude residue which was purified by column chromatography on silica gel (eluant; pet ether:ethyl acetate 9:1) to yield the titled compound **15** (3.04 g, 79%) as an oil. Found: C, 75.00; H, 8.33, $C_{12}H_{16}O_2$ requires C, 74.96; H, 8.39%, ν_{max} (film) 1740 cm^{-1}; λ_{max} (MeOH) 215 nm; δ_H ($CDCl_3$) 1.98 (3H, s, CH_3CO), 2.3 (6H, s, 2 x $ArCH_3$), 3.0 (2H, t, $ArCH_2$), 4.15 (2H, t, CH_2OAc), 6.95 (3H, s, 3 x Ar*H*); δ_C ($CDCl_3$) 19.53 (q), 20.54 (q), 28.7 (t), 62.67 (t), 126.25 (d), 127.99 (d), 133.56 (s), 136.53 (s), 170.72 (s).

*Synthesis of 3-[3-(acetoxyethyl)-2,4-dimethylphenyl]-1-chloro-3-oxopropane **16** and 3-[4-(acetoxyethyl)-3,5-dimethylphenyl]-1-chloro-3-oxopropane **17***

A solution of acetate **15** (2.21 g, 11.5 mmol) in CS_2 (5 ml) was added dropwise to a stirred suspension of $AlCl_3$ (2.3 g, 17.5 mmol) and β-chloropropionylchloride (1.73 g, 13.8 mmol) in CS_2 (20 ml) at 0°C. The resulting tarry mixture was stirred mechanically for 30 min. The mixture was then stirred for 4 h at room temperature. CS_2 was decanted and the reaction residue was added to iced-water. Work-up gave a residue which, after purification by column chromatography (silica gel, pet ether:ethyl acetate 4:1, as eluant) gave **16** and **17** as a 1:1 mixture (2.15 g, 66%). M^+ 284. 0986, $C_{15}H_{19}ClO$ requires 284.0993. ν_{max} (KBr) 1715, 1600 cm^{-1}; δ_H ($CDCl_3$) 2.0 (3H, s, CH_3CO), 2.4 (6H, s, 2 x $ArCH_3$), 3.05 (2H, t, CH_2Ar), 3.3 (2H, t, CH_2Cl), 3.85 (2H, t, CH_2CO), 4.2 (2H, t, CH_2OAc), 7.05 (1H, d, J = 6.8 Hz, Ar*H*) 7.25 (1H, d, J = 6.8 Hz, Ar*H*), 7.6 (1H, s, Ar*H*). Repeated preparative TLC of the isomeric mixture on silica gel (eluant: benzene) yielded **16** as an oil. M^+ 284.0873, $C_{15}H_{19}ClO$ requires 284.0993. ν_{max} (KBr) 1715 cm^{-1}; δ_H ($CDCl_3$) 2.0 (3H, s, CH_3CO), 2.4 (6H, d, 2 x $ArCH_3$), 3.10 (2H, t, CH_2Ar), 3.35 (2H, t, CH_2Cl), 3.85 (2H, t, CH_2CO), 4.2 (2H, t, CH_2OAc), 7.6 (1H, s, Ar*H*).

*General procedure for cyclisation of **16***

A solution of **16** (0.5 g, 1.75 mmol) in concentrated H_2SO_4 (100 ml) was heated at 90°C for 4 h. The reaction mixture was poured cautiously onto ice-water (100 ml) and extracted with ethyl acetate. The organic layer was washed with water (100 ml) and Na_2CO_3 (10%, 100 ml), dried (Na_2SO_4) and evaporated to yield a residue which following chromatography (silica gel; pet ether:ethyl acetate 9:1) yielded 3 products. The least polar compound 6-[2'-chloroethyl]-5,7-dimethyl-indan-1-one **20** was isolated as pale needles. (160 mg, 41%); mp = 94°C (from chloroform-hexane). Lit [8]; mp = 94-95°C. Found M^+ 222.0810, $C_{13}H_{15}ClO$ requires 222.0811.

The second compound eluted from the column was identified as 6-[2-acetoxyethyl]-5,7-dimethylindan-1-one **18** (66 mg, 15%); mp = 63°C. Found M^+ 246.1262, $C_{15}H_{18}O_3$ requires 246.1286. ν_{max} (KBr) 1710, 1605, 1440, 1030 cm^{-1}; λ_{max} (MeOH) 220 nm; δ_H ($CDCl_3$) 2.01 (3H, s, CH_3CO), 2.4 (3H, s, CH_3), 2.65 (3H, s, CH_3), 3.0 (6H, m, 3 x CH_2), 4.1 (2H, t, CH_2OAc), 7.06 (1H, s, ArH); m/z 246 (M^+, 47%), 203(14), 186(100), 173(58), 143(20), 129(12), 115(10), 43(30). The 3rd cyclisation product was identified as 5,7-dimethyl-6-[2'-hydroxyethyl]-indan-1-one **19** (28 mg, 8%); mp = 118°C (needles from hexane); lit [8]; mp = 117-119°C.

*6-[2-Chloroethyl]-2,2,5,7-tetramethylindan-1-one **23** (Pterosin H)*

A solution of **20** (28 mg, 0.11 mmol) in benzene (5 ml) was added dropwise over 15 min to ^{t}BuOK (0.22 mmol) in benzene (20 ml) and ^{t}BuOH (5 ml) and the mixture was stirred at room temperature for 15 min. MeI (0.03 g, 0.22 mmol) was added in 1 portion and the reaction was refluxed gently for 4 h. The benzene was evaporated under vacuum and the residue taken up in ethyl acetate-10% HCl (100 ml). The organic layer was washed with water (100 ml), dried (Na_2SO_4), and evaporated. The residue was purified by prepTLC (pet ether:ethyl acetate 9:1) to yield the titled compound **23**. (27 mg, 85%), as monoclinic crystals; mp = 83-84°C (ethanol); lit [8]; mp = 86-87°C.

*6-[2-methoxyethyl]-2,2,5,7-tetramethylindan-1-one **24** (Pterosin I)*

A solution of **18** (49 mg, 0.19 mmol) in benzene (5 ml) was methylated as for **20** to give a residue which was purified by column chromatography on silica gel (eluant; pet ether:ethyl-acetate 7:3) to yield the titled compound **24** (43 mg, 85%) as needles; mp = 55°C; lit [1]; mp = 56-57°C.

*6-[2-hydroxyethyl]-2,2,5,7-tetramethylindan-1-one **25** (Pterosin Z)*

A solution of **24** (20 mg, 0.08 mmol) was demethylated as for **13** to yield **25** as an oil (7 mg, 35%). M^+ 232 (5%).

*X-ray structure determination of **23***

Suitable single crystals of compound **23** were grown from a saturated solution in ethanol. The intensity data were measured with an Enraf-Nonius CAD4F diffractometer equipped with a graphite monochromator and Mo-K_α' radiation (λ = 0.71069 Å). A crystal with approximate dimensions of 0.3 x 0.3 x 0.25 mm was used for data collection.

Crystal data: $C_{15}H_{19}OCl$, monoclinic, a = 9.078(2) Å, b = 12.968(1) Å, c = 11.802(2)Å, β = 94.17(2), U = 1385.75 $Å^3$, space group $P2_1/c$, Z = 4, F(000) = 536, μ = 34.08 cm^{-1} (range $2° < \theta > 24°$, graphite monochromator, λ = 0.71069 Å, Enraf-Nonius CAD4F diffractometer). The structure was solved by a combination of Patterson search and direct methods, SHELX86 [9], and refined by full matrix least squares using SHELX76 [10] to final values of R = 7.63, R_w = 7.01% with 1109 unique reflections having $I > 3\ \sigma(I)$ and 74 parameters. Data were corrected for Lorentz and polarisation effects but not for absorption. Hydrogen atoms were included in calculated positions with fixed thermal parameters. The chlorine atom was refined anisotropically.

Pharmacological evaluation

Compounds were screened for smooth muscle relaxant activity using isolated guinea pig ileum. Segments of ileum, 2.5 cm in length from guinea pigs of either sex and weighing 300-400 g were suspended in high potassium (45 mM) calcium free modified Kreb's bicarbonated buffer solution, maintained at 37°C and gassed with 95% O_2, 5% CO_2. The composition of the Kreb's solution (g/l) was: NaCl 4.68, KCl 3.35, $MgCl_2$ 0.11, NaH_2PO_4 0.14, $NaHCO_3$ 2.1, glucose 2.0. Isometric contractions were recorded using Grass Ft.03 Force Displacement Transducers and displayed on a Grass 7D Polygraph. Contractures were evoked by an addition of 25 mM $CaCl_2$ and after they had reached a maximum sustained level, compounds were added cumulatively in half-log concentration intervals. ED_{50} values were determined by regression analysis of the linear portion of individual dose-inhibition curves. Statistical comparisons of groups of data was performed using the Mann-Whitney *U*-test, with significance being taken at the $P < 0.05$ level.

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