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# A NEW SYNTHETIC APPROACH TO THE ROTENOID RING SYSTEM

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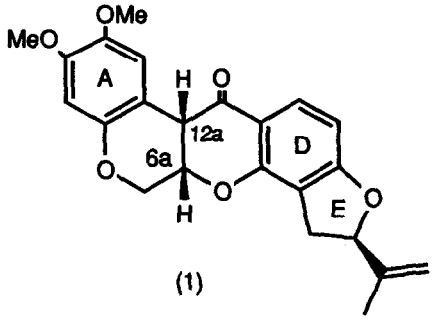
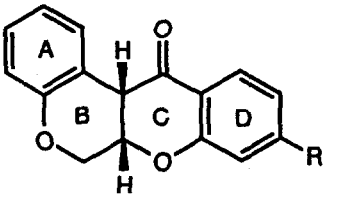
The (±)-cis-chromanochromanones (2) and (3), representing the basic ring system of the natural insecticide rotenone, have been synthesised by a general procedure; the key step is 4-aroylation of the 4-phenyl-sulphonyl)chromans (7; Z=$SO_2$Ph).

Rotenone (1) is the principle insecticide of Derris resin, a natural preparation at one time widely employed in agriculture; it is still utilised as a horticultural and domestic pesticide, and as a piscicide in fish farming. Rotenone blocks mitochondrial electron transport at Complex I in insects, but is biodegradable and is rapidly detoxified in animals, minimising environmental health hazards.[1] This combination of properties has made rotenone an important target for structure-activity studies; however such work has concentrated on compounds derived from the natural series, because of the difficulties associated with total synthesis. To overcome this limitation on the development of the rotenoid group as modern pesticides, new approaches to the chromanochromanone ring system are required, combining brevity with accessible starting materials. We have addressed this problem, and this paper sets out one new strategy, leading to synthesis of the parent rotenoid (2), (formally (±)-6a,12a-dihydro-6H-rotoxen- 12-one)and of its relative (3). Such work is relevant to areas other than agrochemistry, since rotenoids also display antimicrobial and antiviral activity, and are potent inhibitors of SRS-A.

We adopted the strategy set out retrosynthetically in the Scheme. Opening of ring C(4) in the retro-Michael sense would lead to a 4-aroyl-chrom-3-en, further disconnectible to a vinyl anion or its synthetic equivalent. This appeared an attractive prospect since (a) natural rotenoids are known to epimerise at the B/C junction in mild base, with retention of cis-stereochemistry,[2] showing that cis- (4) is thermodynamically preferred to (5); and (b) the vinyl anion equivalent could derive from chroman-4-ones, available in variety. This synthon required an anion stabilising group Z, amenable to elimination as HZ from the putative intermediate (6). Our initial targets were thus chromans (7), and we chose to investigate the series with $R^1$ and $R^2$=H or OMe and with Z=SPh, SOPh, and $SO_2$Ph. We expected that the corresponding chromanones (8) would be easy to access by the well known route[3] from a suitable phenol, via condensation with a β-halopropionate, hydrolysis to an aryloxypropionic acid (9), and cyclisation in acid. These methods work, but the first step is surprisingly low yielding, and we resorted to the addition of phenols to acrylonitrile,

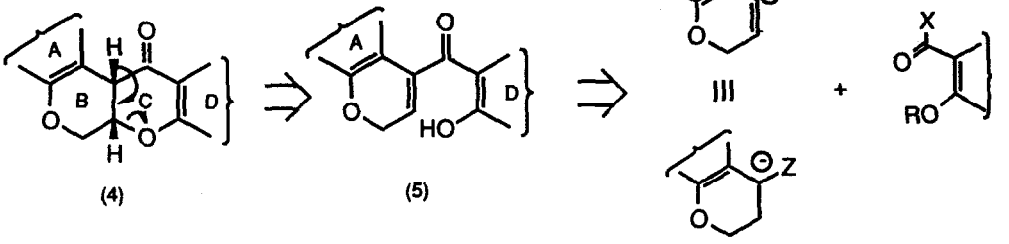



(1)

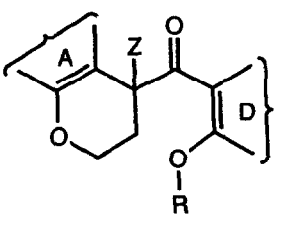



(2) ; R = H

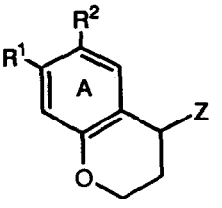
(3) ; R = OMe




Scheme




(6)



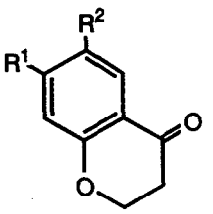

(7)

catalysed by Triton B, which gave nitriles (10), ($R^1$=OMe, $R^2$=H), ($R^1$=H, $R^2$=OMe), ($R^1$=$R^2$=OMe), and ($R^1$=$R^2$=H) in good yield. Hydrolysis to the acids (9) and cyclisation with phosphoric acid to chromanones (8) was straightforward. Alternatively, nitriles (10) could be cyclised directly to chromanones under Houben-Hoesch conditions.[4] The chromanols (7; Z=OH) were simply prepared by borohydride reduction and the desired (phenylthio)chromans (7; Z=SPh) were obtained in good yield from the benzylic alcohols on treatment with thiophenol and zinc iodide.[5] The corresponding sulphoxides and sulphones were prepared through controlled oxidation of the sulphides with MCPBA.

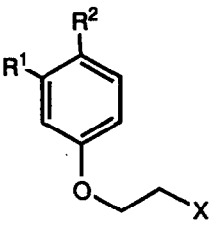
We investigated first the deprotonation of sulphoxide (7; Z=SO.Ph, $R^{1,2}$=H). Reaction with n-butyl lithium afforded the derived anion, as demonstrated by quenching with deuteriated water to give (11; Z=SOPh, R=$^2$H), and with methyl iodide to yield (11; Z=SOPh, R=Me). However all attempts to aroylate the anion with benzoyl chloride, benzoates, or benzonitrile were ineffective; reactions occurred, but we could not detect any of the desired ketones in the product mixtures. Parallel reactions with aryl aldehydes lead chiefly to the benzyl alcohols via Cannizarro reaction. The anion from sulphide (7; Z=SPh, $R^{1,2}$=H) was then investigated: it could be generated using t-butyl lithium, as shown by deuteriation or methylation, to (11; Z=SPh, R=$^2$H and R=Me), but again our efforts at aroylation were unavailing.

However success was achieved with the sulphones (7; Z=$SO_2$Ph). Deprotonation with n-butyl lithium (THF, HMPA) gave an orange anion which could be quenched with methyl iodide, allyl bromide, or benzylbromide, in e.g. the 7-methoxy series, to yield the 4,4-disubstituted chromans (12), (13), and (14). More usefully, aroylation could also be effected with aspirin chloride, 2-methoxybenzoyl chloride, and 2,4-dimethoxybenzoyl chloride, affording the β-ketosulphones (15), (16), and (17) respectively (54-74%). In forming (15) some deacylation was observed which gave rise to (18) as a minor product.

Our relief at finding the solution to the aroylation problem was tempered by the knowledge that the introduction of a 3,4-double bond would now involve elimination of benzenesulphinic acid rather than of benzenesulphenic acid as planned. We found that sulphone (16) was unchanged on refluxing in N,N- diethylaniline or pyridine and with stronger bases e.g. pyrrolidine, smooth retro- Claisen reaction occurred, with efficient regeneration of the starting sulphones. A less direct method for insertion of the essential 3,4-unsaturation thus had to be employed. To this end, the β-ketosulphones (16)-(18) were reductively desulphonylated using Raney nickel in essentially quantitative yield. The product 4-(o-methoxyaroyl)chromans (20) and (21) were dehydrogenated by iodine in ethanol, and the product chrom-3-enes were demethylated (methoxy o to carbonyl) using boron trichloride. The labile intermediates (22) and (23) then were cyclised by

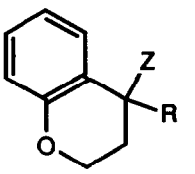


(8)

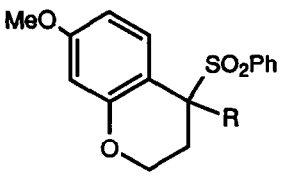


(9) ; X = $CO_2H$

(10) ; X = CN



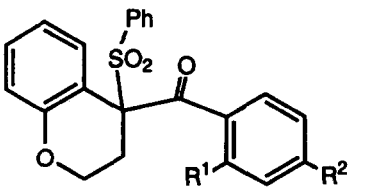
(11)



(12) ; R = Me

(13) ; R = CH.CH=$CH_2$

(14) ; R = $CH_2Ph$

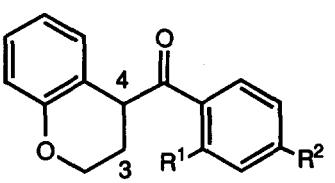


(15) ; $R^1$ = OAc, $R^2$ = H

(16) ; $R^1$ = OMe, $R^2$ = H

(17) ; $R^1$ = $R^2$ = H

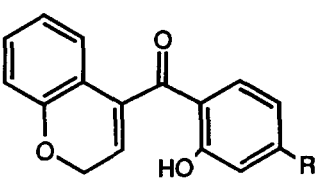
(18) ; $R^1$ = OH, $R^2$ = H



(19) ; $R^1$ = OH, $R^2$ = H

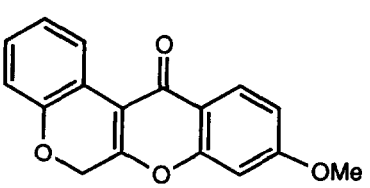
(20) ; $R^1$ = OMe, $R^2$ = H

(21) ; $R^1$ = $R^2$ = OMe

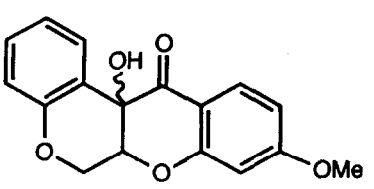


(22) ; R = H

(23) ; R = OMe



(24)



(25)

refluxing in ethanol with potassium acetate to afforded the desired chromano-chromanones (2) and (3) containing the essential rotenoid ring system. In each case the final three steps were executed without purification of intermediates and in modest yield e.g. mean 48% per step for chromano-chromanone (2). Some product losses were suffered through oxidation; thus both (24) and (25) were isolated along with (3). Parallel atmospheric oxidation of natural rotenoids is documented. The target product (2) was identical with an authentic synthetic specimen, whose cis stereochemistry has been proven by $^{1}$H.n.m.r.[6] The thermodynamically preferred cis stereo-chemistry in natural rotenoids has been amply demonstrated by various X-Ray analyses.[7]

A number of synthetic routes to rotenoids have been describe[8] but none are fully satisfactory in terms of overall length and yield, versatility, and compatibility with other desirable substructures. The present route has been shown here to be viable and employs readily accessible starting materials. Further improvements could be made e.g. in the mode of protection of the phenolic hydroxyl involved in the final cyclisation, but the strategy cannot be adapted to enantioselectivity. We are currently concentrating on an alternative route involving kinetic control of B/C stereochemistry and the possibility of asymmetric control.[9]

## EXPERIMENTAL

(1) 3-Aryloxypropanonitriles - The phenol (ca. 0.1 mol), Triton B (1 $cm^3$), and redistilled acrylonitrile (1 mol) were refluxed together under nitrogen for 20 h. The product solution was diluted with chloroform and was washed successively with dil.alkali, dil. acid and water. Evaporation of solvent yielded the product nitriles, (i) 3-phenoxy-propanonitrile, 71%, m.p. 59-60° (lit.[10] m.p. 59-60°), (ii) 3-(3-methoxyphenoxy)propanonitrile, 62%, b.p. 180°C/12 mm (lit.[10] b.p. 146°/3 mm), (iii) 3-(4-methoxyphenoxy) propanonitrile [11], 67%, m.p. 57-59°, and (iv) 3-(3,4-dimethoxyphenoxy) propanonitrile, 74%, m.p. 66-66.5°C (lit.[12] m.p. 66°).

(2) 3-Aryloxypropanoic Acids. - Hydrolysis of the above nitriles in 6M hydrochloric acid at reflux with vigorous stirring for 1.5-3.5 h gave (i) 3-phenoxypropanoic acid, 58%, m.p. 95-96° (lit.[13] 97-98°) (ii) 3-(3-methoxyphenoxy)propanoic acid, 96%, m.p. 82-83° (lit.[14] 81-83°), and (iii) 3-(3,4-dimethoxyphenoxy)propanoic acid, 54%, m.p. 130-131° (lit.[15] m.p. 136-137° for a hydrate).

(3) Chroman-4-ones. - The appropriate nitrile (2-5 g) in dry ether was added to zinc chloride (0.5 g) in dry ether (150 $cm^3$) and hydrogen chloride was bubbled through the mixture at 0° for 5 h. The precipitate was collected and boiled with water (150 $cm^3$) for 1 h. The products were

isolated by chloroform extraction and recrystallised. In this way were obtained (i) 7-methoxychroman-4-one, 51%, m.p. 52-53° (lit.[10] m.p. 52-54°) and (ii) 6,7-dimethoxychroman-4-one, 64%, m.p. 119-120°, (lit.[15] m.p. 123-124°).

(4) 4-(Phenylthio)chromans -

(a) (i) Chroman-4-ol (1.5 g), thiophenol (1.35 g), and zinc iodide (0.4 g) were stirred together in dry 1,2-dichloroethane (20 $cm^3$) in the dark at room temperature under nitrogen for 1 h. Water (20 $cm^3$) was added and the mixture was extracted with dichloromethane. The extracts were washed (aq. alkali, water), dried, and evaporated to yield 4-(phenylthio)chroman, 1.81 g, (87%), b.p. 155-157°, 0.3 mm; (Found: C, 74.7; H, 6.0%; $M^+$ 242.079. $C_{15}H_{14}OS$ requires C, 74.35; H, 5.8%; M, 242.077), $\delta_H$ 1.8-2.4 (2H, m, 3-$H_2$), 4.05-4.65 (3H, m, 2-$H_2$, 4-H), 6.57-7.0 (2H, m, 6-H, 8-H), and 7.05-7.55 (7H, m, ArH).

(ii) Thiophenol (11.45 g) was added dropwise to sodium hydride (2.5 g) suspended in dry DMF (50 $cm^3$) under nitrogen at 0°. When hydrogen evolution ceased, 4-chlorochroman (17.4 g, from chroman-4-ol and thionylchloride over 7 h. at ambient temperature) was added dropwise. Potassium iodide (0.5 g) was then added and the mixture was stirred for 48 h at ambient temperature. Product isolation as in 4a(i) yielded 4-(phenylthio) chroman (20 g, 80%), identical with the above sample.

(b) 7-methoxychroman-4-ol (1.42 g: from reduction of 7-methoxychromanone with sodium borohydride in ethanol, room temperature, 2.5 h) was stirred in dichloromethane (40 $cm^3$) with thiophenol (1.4 g) and zinc iodide (0.5g) for 2 h at ambient temperature in the dark under nitrogen. Product isolation as in expt.4a(i), but using ether, gave 7-methoxy-4-(phenyl thio)chroman, (1.95 g, 91%), m.p. 61-62°; (Found: C, 70.95; H, 6.0%, $M^+$ 272.087. $C_{16}H_{16}O_2S$ requires C, 70.55; H, 5.9%; M, 272.087); $\delta_H$ 2.0 (1H, ddd, J 14.5, 5.6, 2.7 Hz), 2.15-2.29 (1H, m), 3.76 (3H, s, OMe), 4.18-4.26 (1H, m), 4.46-4.55 (2H, m), 6.36 (1H, d, J 2.6, 8-H), 6.49 (1H, dd, J 8.6, 2.6, 6-H), and 7.22-7.47 (6H, m, ArH).

(c) (i) 6,7-Dimethoxychromanone was reduced with excess sodium borohydride in ethanol at ambient temperature for 3.5 h; standard isolation procedures gave 6,7-dimethoxychroman-4-ol, (62%) m.p. 81-82° from chloroform-cyclohexane; (Found: C, 63.1; H, 6.75%; $M^+$ 210.088. $C_{11}H_{14}O_4$ requires C, 62.85; H, 6.7%; M, 210.089).

(ii) 6,7-Dimethoxchroman-4-ol (380 mg) was reacted with thiophenol (500 mg) in 1,2-dichloromethane (5 $cm^3$) and zinc iodide (0.5 g) for 3 h. Product isolation as in expt. 4a(i) gave

6,7-dimethoxy-4-(phenylthio)chroman (500 mg, 92%) as an oil (single t.l.c. spot); (Found: $M^+$ 302.096. $C_{17}H_{18}O_3S$ requires M, 302.098); $\delta_H$ 1.82-2.45 (2H, m, 3-$H_2$), 3.70 and 3.74 (each 3H, s, OMe), 4.05-4.6 (3H, m, 2-$H_2$, 4-H), 6.41 (1H, s, 8-H), 6.8 (1H, s, 5-H), and 7.35-7.6 (5H, m, ArH).

(5) (4-Phenylsulphinylchroman. - 4-Phenylthiochroman (5.7 g) in dry dichloromethane (80 $cm^3$) was treated at 0°C with MCPBA (4.27 g in portions over 10 min. The solution was set aside at ambient temperature under nitrogen for 9 h., filtered, washed (aq. sodium metabisulphite, aq. bicarbonate, brine), and dried. Evaporation gave the title compound as a pair of diastereoisomers (5.35 g, 81%), (Found: C, 69.9; H, 5.2. $C_{15}H_{14}O_2S$ requires C, 69.75; H, 5.4%). Crystallisation from ether gave one diastereoisomer, decomp. on heating, $\delta_H$ 2.0-2.4 (1H, m), and 2.6-2.9 (1H, m), 3-$H_2$), 3.75-3.9 (1H, m) and 4.3-4.7 (2H, m), (2-$H_2$ and 4-H), 6.4 (1H, dd, J 2, 7.5 Hz, 8-H), 6.6-6.95 (2H, m, ArH), 7.05-7.3 (1H, m, ArH), and 7.55 (5H, bs, Ph).

(6) 4-(Phenylsulphonyl)chromans. -

(a) (i) 4-(Phenylthio)chroman (4.2 g) in dry dichloromethane (250 $cm^3$) was treated with MCPBA (6.6 g) as above, but for 18 h. Product isolation as in (5) gave 4-(phenylsulphonyl)chroman, (3.85 g, 81%) as prisms from methanol m.p. 86.5-87°; (Found: C, 65.85; H, 5.3%; $M^+$ 274.065. $C_{15}H_{14}O_3S$ requires C, 65.65; H, 5.15%; M, 274.066); $\delta_H$ 2.17-2.32 (1H, m) and 2.52 (1H, ddd, J 2.7, 5.3, and 15.3 Hz), (3-$H_2$), 4.13-4.23 (1H, m, 2-Ha), 4.3-4.4 (2H, m, 4-H, 2-Hb), 6.78-6.86 (2H, m, 6-H and 8-H), 7.06 (1H, dd, J 1.6 and 7.6 Hz, 5-H), 7.2-7.3 (1H,m,7-H), 7.5-7.9 (5H, Ph). (ii) Chroman-4-ol (1.35 g) and sodium benzene sulphinate (3 g) were heated together in formic acid (98-100%) (100 $cm^3$), on steam, for 3 h. Product isolation by dilution with water and ether extraction gave the sulphone (1.48 g, 61%), indistinguishable from the above specimen.

(b) 7-Methoxy-4-(phenylthio)chroman (2.4 g) in dichloromethane (70 $cm^3$) was treated with MCPBA (3.5 g) as in expt. (5), for 2.5 h. After evaporation of the solvent the residue was dissolved in ethyl acetate. The solution was washed as in expt.5 and evaporated; the residue was chromatographed on silica using hexane-ethyl acetate (4:1), to afford the 7-methoxy-4-(phenylsulphonyl)chroman (1.21 g, 45%), prisms from ethanol m.p. 110-111°C; (Found: C, 63.25; H, 5.35%; $M^+$ 304.081. $C_{16}H_{16}O_4S$ requires C, 63.15; H, 5.3%; $M^+$ 304.077); $\delta_H$ (250 MHz) 2.13-2.19 (1H, m) and 2.48 (1H, ddd, J 2.7, 5.2, and 15.3 Hz) (3-$H_2$), 3.76 (3H, s, OMe), 4.12-4.19 (1H, m, 2-Ha), 4.25-4.37 (2H, m, 4-H, 2-Hb), 6.37 (1H, d, J 2.6 Hz, 8-H),

6.41 (1H, dd, J 2.6, 8.5 Hz, 6-H), 6.94 (1H, d, J 8.5, 5-H), and 7.5-7.8 (5H, Ph).

(c) 6,7-Dimethoxy-4-(phenylthio)chroman (370 mg) in dry dichloromethane (25 $cm^3$) was treated with m-chloroperbenzoic acid (450 mg) as in exp.(6b). Product isolation in the same fashion gave 6,7-dimethoxy-4- (phenylsulphonyl)chroman (196 mg, 48%), m.p. 137.5-138.5°C from ethanol; (Found: C, 60.8; H, 5.5%; $M^+$ 331.084. $C_{17}H_{18}O_5S$ requires C, 61.05; H, 5.45%; $M^+$ 334.087); $\delta_H$ (250 MHz) 2.15-2.3 (1H, m) and 2.53 (1H, ddd, J 2.8, 5.3, 15.3 Hz), (3-$H_2$), 3.64 and 3.83 (both 3H, s, OMe), 4.09-4.17 (1H, m, 2-Ha), 4.21-4.31 (2H, m, 4-H, 2-Hb), 6.38 (1H, s, 8-H), 6.47 (1H, s, 5-H), 7.52-7.81 (5H, Ph).

(7) 4-Methyl-4-(Phenylthio)chroman. - 4-(Phenythio)chroman (140 mg) in dry THF (3 $cm^3$) with dry HMPA (1 $cm^3$) was cooled to -75°C under nitrogen, and treated with t-butyllithium (2.2M in pentane, 0.3 $cm^3$), with stirring. An orange-red colour developed. After 5 min. freshly distilled methyl iodide (1 $cm^3$) was added, and the mixture became colourless. The reaction temperature was allowed to rise to ambient, overnight, and the mixture was then diluted with aq. ammonium chloride (10 $cm^3$) and extracted with ether. The extractives were chromatographed on silica using chloroform-hexane (1:3) to yield the title compound (40 mg, 27%) as a colourless oil (Found: $M^+$ 256.093. $C_{16}H_{16}OS$ requires $M^+$ 256.092); $\delta_H$ 1.7 (3H, s, Me), 2.0-2.2 (2H, m, 3-$H_2$), 4.1-4.4 (1H, m) and 4.5-4.7 (1H, m) (2-$H_2$), 6.8-7.05 (2H, m, 6-H, 8-H), 7.1-7.6 (7H, ArH). The product showed only one spot on t.l.c., and no additional $^1H$ n.m.r. peaks.

(8) Alkylation of 4-(Phenylsulphonyl)chromans. -

(a) 4-(Phenylsulphonyl)chroman (434 mg) in dry THF (5 $cm^3$) with HMPA (0.7 $cm^3$) was cooled under nitrogen to -75°C, and treated with n-butyllithium (1.7M, 1 $cm^3$). After 5 min. methyliodide (1 $cm^3$) was added to the orange solution, which decolourised. The mixture was allowed to warm to room temperature, over 4 h., when the products were isolated as in expt.(7). Chromatography using ethyl acetate-hexane (1:4) gave 4-methyl-4-(phenylsulphonyl) chroman (241 mg, 53%), prisms from methanol m.p. 107-109°C; (Found: C, 66.4; H, 5.5%; $M^+$ 288.079. $C_{16}H_{16}O_3S$ requires C, 66.65; H, 5.6%; $M^+$ 288.082); $\delta_H$ 1.82 (3H, s, Me), 1.85-2.25 (1H, m) and 2.45-2.75 (1H, m) (3-$H_2$), 3.9-4.5 (2H, m, 2-$H_2$), 6.75-7.1 (2H, m, 6-H, 8-H), 7.15-7.8 (7H, ArH). In similar fashions were prepared 7-methoxy-4-methyl-4- (phenylsulphonyl)chroman (50%), m.p. 105-106° from methanol; (Found: C, 64.1; H, 6.0. $C_{17}H_{18}O_4S$ requires C, 64.15; H, 5.7%), and 6,7-dimethoxy-4-methyl-4-methyl-4-(phenyl-sulphonyl)chroman (42%), as a gum; (Found: C, 62.4; H, 5.6. $C_{18}H_{20}O_5S$ requires C, 62.05; H, 5.75%).

(b) 7-Methoxy-4-(phenylsulphonyl)chroman (137 mg) was treated at -75° with n-butyllithium (1.5M, 0.4 $cm^3$) as described in exp.(7). The orange anion was quenched with allyl bromide (0.5 $cm^3$). After 2 h. the product was isolated as above, and purified by chromatography (ethyl acetatehexane, 1:4) to afford 4-allyl-7-methoxy-4-(phenylsulphonyl)chroman (52%) as a gum, one spot t.l.c; (Found: $M^+$ 344.108. $C_{19}H_{20}O_4S$ requires $M^+$ 344.108); $\delta_H$ 2.2-2.6 (2H, m, 3-$H_2$), 2.65-2.9 (1H, m) and 3.15-3.45 (1H, m) ($CH_2$.CH=$CH_2$), 3.82 (3H, s, OMe), 3.9-4.3 (2H, m, 2-$H_2$), 5.0-5.65 (3H, -CH=$CH_2$), 6.38 (1H, d, 8-H), 6.66 (1H, dd, 6-H), 7.42 (1H, d, 5-H), and 7.45-7.8 (5H, Ph).

(c) In an experiment closely similar to (8b) above, benzyl chloride was substituted for allyl bromide, to provide, after chromatography (ethyl acetate-hexane, 1:4) and crystallisation from methanol, 4-benzyl-7-methoxy-4-(phenylsulphonyl)chroman, m.p. 117-119°C, $\delta_H$ 2.15-2.45 (1H, m) and 2.9-3.2 (1H, m), (3-$H_2$), 3.43 (1H, d, J 14, Ph-$CH_a$), 3.15-4.05 (6H, OMe, 2-$H_2$, Ph-$CH_b$), 6.24 (1H, d, 8-H), 6.75 (1H, dd, 6-H), 6.85-7.75 (10H, ArH), and 7.94 (1H, d, 5-H).

(9) Aroylation of 4-(Phenylsulphonyl)chromans. -

(a) 4-Phenylsulphonylchroman (616 mg) in dry THF (10 $cm^3$) and HMPA (3 $cm^3$) was treated, under nitrogen at -75°C, with n-butyllithium (1.6M, 1.5 $cm^3$). The orange solution was stirred for 5 min., when 2-acetoxybenzoyl chloride (731 mg) in THF (5 $cm^3$) was added dropwise. The mixture was allowed to warm to ambient temperature overnight, quenched with aq. ammonium chloride (30 $cm^3$) and extracted with ethyl acetate. The washed organic phases were evaporated and the residue crystallised from ethanol to yield 4-(2-acetoxybenzoyl)-4-(phenylsulphonyl)chroman (527 mg, 54%) m.p. 153-154°C; (Found: C, 66.0; H, 4.75%; $M^+$ 436.095. $C_{24}H_{20}O_6S$ requires C, 66.05; H, 4.6%; $M^+$ 436.098); $\lambda_{max}$ 276 (3.55), 293 (3.52), and 321i (287) nm; $\nu_{max}$ 1765, 1695, 1605 and 1580 $cm^{-1}$; $\delta_H$ (250 MHz) 2.03 (3H, s, Me), 2.59-2.81 (2H, m, 3-$H_2$), 4.09-4.17 (1H, m) and 4.51-4.61 (1H, m), (2-$H_2$), and 6.73-7.88 (13H, ArH).

(b) Using very similar methods, with 2-methoxybenzoyl chloride, gave 4-(methoxybenzoyl)-4-(phenylsulphonyl)chroman (74%), m.p. 162-163° from ethanol; (Found: C, 67.65; H, 5.15%; $M^+$ 408.153. $C_{23}H_{20}O_5S$ requires C, 67.65; H, 4.95%; $M^+$ 408.103); $\delta_H$ (250 MHz) 2.53 (1H, ddd, J 3.5, 7.7, 14.7, 3-$H_a$), 2.73 (1H, ddd, J 3.3, 14.7, 3-$H_b$), 3.20 (3H, s, OMe), 4.16 (1H, ddd, J 3.3, 7.7, 11.1, 2-$H_a$), 4.40 (1H, ddd, J 3.5, 7.3, 11.1, 2-$H_b$), 6.50-7.88 (12H, ArH).

Another reaction using 2,4-dimethoxybenzoyl chloride afforded

(c) 4-(2,4-dimethoxybenzoyl)-4-phenylsulphonyl) chroman (63%), m.p. 154-155° from ethanol; (Found: C, 65.7; H, 5.05%; $M^+$ 438.115.

$C_{24}H_{22}O_6S$ requires C, 65.75; H, 5.05%; $M^+$ 438.114); $\delta_H$ (250 MHz) 2.52 (1H, ddd, J 3.2, 6.2, 14.9, 3-$H_a$), 2.77 (1H, ddd, J 3.8, 8.9, 14.9, 3-$H_b$), 3.18 (3H, s, OMe), 3.79 (3H, s, OMe), 4.20 (1H, ddd, J 3.8, 6.2, 11.1, 2-$H_a$), 4.50 (1H, ddd, J 3.2, 8.9, 11.1, 2-$H_b$), 6.04 (1H, d, J 2.2, ArH), 6.51 (1H, dd, J 2.2, 8.5, ArH), 6.62 (1H, ddd, J 1.2, 7.7, 7.7, 6-H), 6.87 (1H, dd, J 1.2, 8.2, 8-H), 7.13-7.21 (2H, m, 5-H, 7-H), 7.37 (1H, d, J 8.5, ArH), and 7.5-7.9 (5H, m, Ph).

(d) Using the methodology of expt. (9a), 7-methoxy-4-(phenylsulphonyl) chroman (292 mg) was deprotonated and reacted with 2,4-dimethoxybenzoyl chloride (571 mg), to afford 4-(2,4-dimethoxybenzoyl)-7-methoxy-4-(phenylsulphonyl)chroman, m.p. 116-117° from methanol, $\delta_H$ 2.4-2.9 (2H, m, 3-$H_2$), 3.3, 3.77, and 3.81 (each 3H, s, OMe), 4.0-4.3 (1H, m, 2-$H_a$), 4.35-4.65 (1H, m, 2-$H_b$), 6.14 (1H, d, J 3, 8-H), 6.28 (1H, dd, J 3, 9, 6-H), 6.4-6.6 (2H, m, ArH), 7.16 (1H, d, J 9, 5-H), 7.38 (1H, d, J 9, ArH), 7.55-7.75 (3H, m, ArH), and 7.9-8.05 (2H, m, ArH).

(10) Desulphonylations

(a) To a vigorously stirred solution of 4-(2-salicoyl)-4-(phenylsulphonyl)chroman (144 mg, from deacylation with lithium hydroxide of the corresponding acetate) in ethyl acetate (40 $cm^3$) was added Raney nickel (W3) in portions (ca. 250 mg) every 30 min. over 4 h. The mixture was filtered and the filtrate was evaporated to yield 1-(2-hydroxybenzoyl)chroman (98%) as a gum (1 spot t.l.c.) (Found: C, 75.7; H, 5.9. $C_{16}H_{14}O_3$ requires C, 75.6; H, 5.6%); $\nu_{max}$ 1640 $cm^{-1}$; $\delta_H$ (250 MHz) 2.20-2.45 (2H, m, 3-$H_2$), 4.15-4.33 (2H, m, 2-$H_2$), 4.86-4.91 (1H, m, 4-H), 6.81-7.24 (6H, m, ArH), 7.53 (1H, ArH), 7.90 (1H, ArH), and 12.33 (1H, s, OH).

(b) In a similar manner was prepared 4-(2-methoxybenzoyl)chroman (99%), redistilled bulb-to-bulb at 160°C, 0.1 mm; (Found: C, 75.95; H, 6.40%; $M^+$ 268.112. $C_{17}H_{16}O_3$ requires C, 76.1; H, 6.0%; $M^+$ 268.110); $\delta_H$ (250 MHz) 2.19-2.26 (2H, m, 3-$H_2$), 3.92 (3H, s, OMe), 4.18-4.30 (2H, m, 2-$H_2$), 4.78-4.82 (1H, 4-H), 6.76-7.16 (6H, m, ArH), and 7.45-7.55 (2H, m, ArH): and 4-(2,4-dimethoxybenzoyl)-chroman (99%), m.p. 106.5-108°C from methanol; (Found: C, 72.50; H, 6.20%; $M^+$ 298.119. $C_{18}H_{18}O_4$ requires C, 72.45; H, 6.1%; $M^+$ 298.121); $\delta_H$ 2.17-2.26 (2H, m, 3-$H_2$), 3.87 and 3.91 (each 3H, s, OMe), 4.16-4.29 (2H, m, 2-$H_2$), 4.86-4.90 (1H, m, 4-H), 6.50 (1H, d, J 2.2, ArH), 6.55 (1H, dd, J 2.2 and 8.6, ArH), 6.77-6.87 (2H, m, 6-H, 8-H), 6.92-6.96 (1H, m, 5-H), and 7.09-7.15 (1H, m, 7-H).

(11) (±)-6a,12a-Dihydro-6H-Rotoxen-12-one - 4-(2-Methoxybenzoyl)chroman (140 mg) was refluxed in ethanol (15 $cm^3$) with iodine (300 mg) and anhydrous potassium acetate (750 mg) for 2 h. The mixture was evaporated and the residue was triturated with ether. The solution was washed (aq. sodium

thiosulphate, aq. sodium bicarbonate), dried, and evaporated to yield 4-(2-methoxybenzoyl)-2H-chromen, $\delta_H$ 3.74 (3H, s, OMe), 4.82 (2H, d, J 4, 2-$H_2$), 6.30 (1H, t, J 4, 3-H), and 6.75-7.8 (8H, ArH). Without further purification the chromene in dichloromethane (2 $cm^3$) was treated with boron trichloride (0.45 $cm^3$, 2M in dichloromethane) at 0°. The mixture was set aside at room temperature for 50 min and quenched with water. The organic products were collected via ether extraction and refluxed under nitrogen in ethanol (20 $cm^3$) saturated with potassium acetate for 2.5 h. Dilution with water and extraction with ether provided an oil which was chromatographed, on silica (ethyl acetate-hexane, 1:4). The major fraction crystallised from methanol-ether to yield the title compound (15 mg; equivalent overall to a 48% yield at each of the three steps), m.p. 161.5-163°C, lit.[6] m.p. 163°, (Found: C, 76.05; H, 4.80%; $M^+$ 252.079. Calc. for $C_{16}H_{12}O_3$ C, 76.2; H, 4.80%; $M^+$ 252.079). The sample had i.r., u.v., and $^1$H.n.m.r. spectra indistinguishable from those of authentic material.[6]

(12) (+)-6a,12a-Dihydro-9-Methoxy-6H-Rotoxen-12-one. - 4-(2,4-Dimethoxybenzoyl) chroman (317 mg) in ethanol 30 $cm^3$) was refluxed with iodine (700 mg) and potassium acetate (1.5 g). The crude chromen product was isolated as in expt.(11), with $\delta_H$ 3.65 and 3.86 (each 3H, s, OMe), 4.84 (2H, d, J 4, 2-$H_2$), 6.17 (1H, t, J 4, 3-H), and 6.42-7.67 (7H, ArH). Demethylation and cyclisation were effected as described above (expt.11) to yield the title compound (13 mg, equivalent to a 35% yield at each of three steps), m.p. 150-151° from methanol-ether; (Found: C, 72.20; H, 5.05%; $M^+$ 282.088. $C_{17}H_{14}O_4$ requires C, 72.35; H, 5.0%; $M^+$ 282.089); $\nu_{max}$ 1670, 1605, 1580 $cm^{-1}$; $\delta_H$ (250 MHz) 3.78 (3H, s, OMe), 3.91 (1H, m, 12a-H), 4.24 (1H, ddd, J 1,1,12.2 Hz, 6-Ha), 4.65 (1H, dd, J 3.1, 12.2 Hz, 6-Hb), 4.95-4.98 (1H, m, 6a-H), 6.40 (1H, d, 8-H), 6.40 (1H, d, 8-H), 6.56 (1H, dd, 10-H), 6.83-7.27 (4H, ArH), and 7.68 (1H, d, 11-H).

Also isolated, arising from air oxidation of the rotenoid during manipulation, were 9-methoxy-6H-rotoxen-12-one, (Found: $M^+$ 280.074. $C_{17}H_{12}O_4$ requires $M^+$ 250.074); $\delta_H$ (250 MHz) 3.91 (3H, s, OMe), 5.03 (2H, s, 6-$H_2$), 6.84 (1H, d, J 2.4 Hz, 8-H), 6.94-7.26 (5H, ArH), 8.21 (1H, d, J 8.8 Hz, 11-H) and 8.77 (1H, dd, J 1.7, 7.8 Hz, 1-H) and (+)-6a,12a-dihydro-12a- hydroxy-9-methoxy-6H-rotoxen-12-one; (Found: $M^+$ 298.081. $C_{17}H_{14}O_5$ requires $M^+$ 298.084); $\delta_H$ 3.78 (3H, s, OMe), 4.50 (1H, bs, OH), 4.52-4.69 (3H, m, 6-$H_2$, 6a-H), 6.37 (1H, d, 8-H), 6.59 (1H, dd, 10-H), 6.84 (1H, m, 2-H), 6.96 (1H, dd, 4-H), 7.09 (1H, dd, 1-H), 7.23 (1H, m, 3-H), and 7.85 (1H, d, 11-H).

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