

Synthesis of 4-Hydroxycoumarin Derivatives-1: An Efficient Synthesis of Flocoumafen

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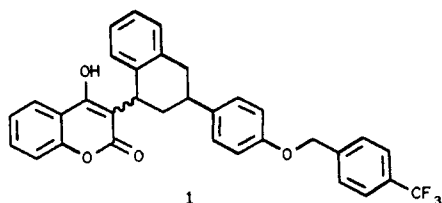
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An anticoagulant, 4-hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl]coumarin (Flocoumafen) was synthesized in 8 steps starting from phenylacetyl chloride and anisole. The key step in the synthesis involves the reaction of 3-(4-methoxyphenyl)-1-tetralol with 4-hydroxycoumarin to give 4-hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-methoxyphenyl)-1-naphthyl]coumarin.

Key words : 4-Hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl]coumarin (Flocoumafen), Anticoagulant, Rodenticide, Phenylacetyl chloride, Anisole

INTRODUCTION

4-Hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl]coumarin (**1**) is known as having potent anticoagulant properties and has been used successfully as rodenticide (Rowe *et al.*, 1985; Buckle 1986; Parshad and Chopra 1986; Parshad 1988). As rodenticide, it is particularly effective (Entwistle and Boehm 1986) against rodents resistant to such agents as Warfarin, Coumatetralyl, Diphacinone and Pival. We report here a simple and efficient synthesis of 4-hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl] coumarin (**1**), from commercially available starting materials in 25% overall yield.



The efficient synthetic route to 4-hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl]coumarin (**1**) is outlined in the following scheme 1.

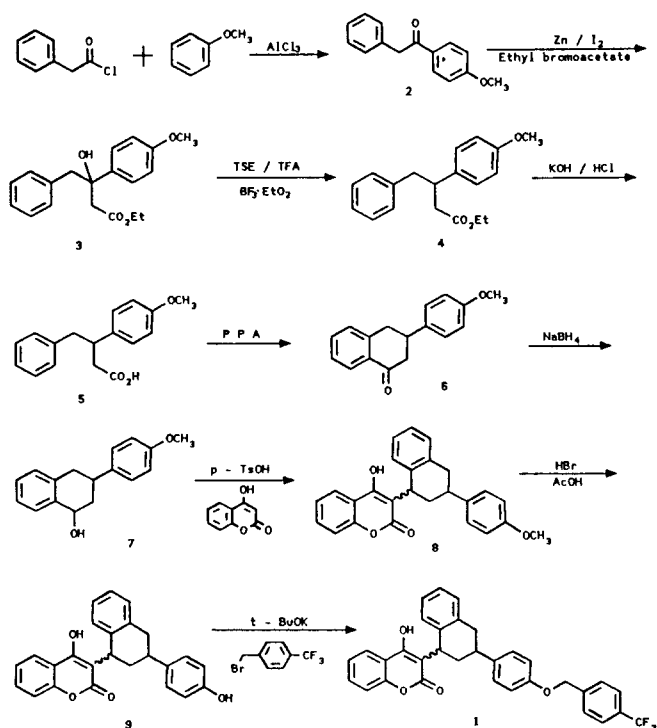
MATERIALS AND METHODS

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Reactions requiring anhydrous conditions were performed with the usual precautions for rigorous exclusion of air and moisture. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl prior to use. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F₂₅₄ plates from EM reagents and visualized with 254-nm UV light or ceric sulfate-ammonium molybdate-sulfuric acid spray. Flash chromatography was carried out on silica gel 60 (E. M. Merck, particle size 0.040~0.063 mm, 230~400 mesh ASTM). The ¹H NMR spectra were recorded on a Bruker AC 80 (80 MHz) and/or Varian Gemini 200 (200 MHz) NMR spectrometer. The chemical shifts were reported in parts per million (ppm) downfield from tetramethylsilane, and J-values were in Hz. IR spectra were obtained on a Perkin-Elmer Model 782 spectrometer. Mass spectra were recorded on a Shimadzu-LKB 9000 GC/MS system. All mps were uncorrected. When necessary, chemicals were purified according to the reported procedure (Perrin *et al.*, 1980).

1-(4-Methoxyphenyl)-2-phenyl-1-ethanone (2).

Phenylacetyl chloride (10 g, 0.65 mmol) and anisole (73.4 g, 0.68 mol) were dissolved in dichloromethane (600 ml) and cooled in ice-salt bath. To this solution was added AlCl₃ (94.6 g, 0.71 mol) keeping the temperature under -10°C. The reaction mixture was stirred for 16 h while the temperature was kept under -10°C. The reaction mixture was poured to aqueous HCl solution and extracted with dichloromethane (three times). The combined extracts were washed with a brine, dried over MgSO₄ and then concentrated under reduced



Scheme 1

pressure. The crude residue obtained was recrystallized from methanol to give a white crystalline solid (129.8 g, 89%); mp 71–73°C; IR (KBr) 1675, 1595, 1205 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 80 MHz), δ 3.84 (s, 3 H), 4.22 (s, 2 H), 6.91 (d, $J=8.5$ Hz, 2 H), 7.22–7.34 (m, 5 H), 8.00 (d, $J=8.5$ Hz, 2 H).

Ethyl 3-hydroxy-3-(4-methoxyphenyl)-4-phenylbutanoate (3).

Ketone **2** (1.34 g, 5.9 mmol) and zinc (0.43 g, 6.5 mmol) were added to benzene (10 ml) and refluxed for 1 h. To this mixture, were added ethyl bromoacetate (1.09 g, 6.5 mmol) and iodine (5 mg) in benzene and refluxed for 1 h. After cooling to RT, 15% H_2SO_4 solution was added to separate organic-aqueous layer. The organic layer was washed with a 10% sodium carbonate solution and water (three times), dried over anhydrous MgSO_4 , and then concentrated under reduced pressure to afford the crude product **3** (179.8 g, 96.6%) which was pure enough for the next reaction; IR (KBr) 3475, 1700, 1595, 1505, 1250, 1165, 1025 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 80 MHz) δ 1.08 (t, $J=7.14$ Hz, 3 H), 2.83 (d, $J=8.50$ Hz, 2 H), 3.07 (s, 2 H), 3.67 (s, 3 H), 3.90 (q, $J=7.14$ Hz, 2 H), 4.45 (s, 1 H), 6.73 (d, $J=8.79$ Hz, 2 H), 7.13 (s, 5 H), 7.33 (d, $J=8.79$ Hz, 2 H).

Ethyl 3-(4-methoxyphenyl)-4-phenylbutanoate (4).

To a solution of alcohol (2.59 g, 8.2 mmol) in di-

chloromethane (10 ml) was added triethylsilane (1.06 g, 9.1 mmol), trifluoroacetic acid (3.76 g, 33 mmol) and boron trifluoride (0.03 ml). This mixture was refluxed for 8 h, and washed with a 30% potassium carbonate. The organic layer was washed with water (three times), dried over anhydrous MgSO_4 and then concentrated under reduced pressure to afford the desired product (2.43 g, 90%); IR (KBr) 1700, 1595, 1235, 1205 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 80 MHz) δ 1.10 (t, $J=7.4$ Hz, 3 H), 2.55 (d, $J=7.4$ Hz, 2 H), 2.84 (d, $J=7.4$ Hz, 2 H), 3.34 (quintet, $J=7.4$ Hz, 1 H), 3.73 (s, 3 H), 3.96 (q, $J=7.4$ Hz, 2 H), 6.63–7.50 (m, 9 H).

3-(4-Methoxyphenyl)-4-phenylbutanoic acid (5).

The mixture of ethyl butanoate **4** (5.0 g, 0.02 mol), sodium hydroxide (4.3 g, 0.08 mol) and water (15 ml) were refluxed for 8 h. After cooling to RT, benzene was added to the residue. The aqueous layer was acidified with a 10% HCl solution (PH=1–2) and extracted with dichloromethane. The organic layer was washed with water, dried over MgSO_4 and concentrated under reduced pressure to afford the crude product. The crude product was recrystallized from ethyl acetate to give the desired compound **5** as a pale yellow crystalline powder (5.0 g, 92%); mp 122–125°C (lit. mp 120–121°C; Selvaraj *et al.*, 1987); IR 1700, 1510, 1235, 1025 cm^{-1} ; $^1\text{H NMR}$ (CDCl_3 , 200 MHz) δ 2.61 (m, 2 H), 2.86 (d, $J=7.50$ Hz, 2 H), 3.33 (q, $J=7.41$ Hz, 1 H), 3.76 (s, 3 H), 6.78 (d, $J=8.57$ Hz, 2 H), 7.02–7.05 (m, 4 H), 7.15–7.23 (m, 3 H), 11.5 (br s, 1 H).

3-(4-Methoxyphenyl)-1-tetralone (6).

Method A: To polyphosphoric acid (24.0 g) in 80°C was added butanoic acid (24.0 g, 22 mmol) portionwise with stirring. After stirring for 1 h at this temperature, the reaction mixture was cooled to RT and extracted with dichloromethane. The organic layer was washed with a 10% sodium carbonate solution and water, dried over MgSO_4 and concentrated under reduced pressure to afford the crude product. The crude product was recrystallized from methanol to give the desired product (4.76 g, 85%)

Method B: The cooled solution of butanoic acid (6.0 g, 22 mmol) in benzene (20 ml) with ice-water bath, was added phosphorus pentachloride (9.3 g, 45 mmol) portionwise. When phosphorus pentachloride was dissolved completely, the ice-water bath was removed and refluxed for 1 h. The reaction mixture was cooled with ice-water bath and stannic chloride (15.6 g, 60 mmol) in benzene was added. After the resulting mixture was stirred at 0–10°C for 1 h, ice and water were added. The resulting mixture was extracted with ether (three times). The organic layer was

treated in the same manner as Method A., to afford the desired product (4.75 g, 85%); mp 102~105°C (lit. mp 105-106°C; Selvaraj *et al.*, 1987); IR (KBr) 1675, 1505, 1245, 1025 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 2.67-3.03 (m, 2 H), 3.03-3.40 (m, 3 H), 3.80 (s, 3 H), 6.83 (d, J=10 Hz, 2 H), 7.07-7.73 (m, 5 H), 7.90-8.30 (m, 1 H)

3-(4-Methoxyphenyl)-1-tetralol (7).

To a suspension of tetralone (5.0 g, 20 mmol) in ethanol (20 ml) was added sodium borohydride (839 mg, 24 mmol) portionwise. After stirring at RT for 2 h, the reaction mixture was diluted with water, acidified with 20% HCl solution and extracted with dichloromethane (three times). The combined extracts were washed successively with water, NaHCO₃ solution and water, dried over MgSO₄ and then concentrated under reduced pressure. Chromatography of the crude product on silica gel (1 : 8 ethyl acetate/hexane) gave the desired compound **7** (4.39 g, 87%) as a white crystalline solid; mp 107~109°C; IR (KBr) 3350, 1605, 1505, 1250, 1025, 735 cm⁻¹; ¹H NMR (CDCl₃, 200 MHz) δ 1.82-1.96 (m, 2 H), 2.43-2.50 (m, 1 H), 2.91-3.10 (m, 3 H), 3.81 (s, 3 H), 4.98 (dd, J=10.30, 5.83 Hz, 1 H), 6.89 (d, J=8.57 Hz, 2 H), 7.15 (d, J=7.42 Hz, 1 H), 7.19-7.28 (m, 4 H), 7.62 (d, J=7.42 Hz, 1 H).

cis-(8a) and *trans*-(8b) 4-Hydroxy-3-[1,2,3,4-tetrahydro-3-(4-methoxyphenyl)-1-naphthyl]coumarin.

Sulphuric acid (80%, 3.4 ml) was added dropwise with stirring to a mixture of 4-hydroxycoumarin (8.1 g, 50 mmol), tetralol **7** (12.6 g, 50 mmol) and acetic acid (25 ml) at 105°C. The mixture was stirred and heated at 110°C for 3 h, then diluted with water and extracted with dichloromethane (three times). The organic phase was extracted with dilute sodium hydroxide solution (three times) and the combined alkaline extracts were acidified and extracted with dichloromethane (three times). The dichloromethane extracts were washed with water, dried over MgSO₄ and then concentrated under reduced pressure to afford the crude product, showing two spots on TLC owing to the presence of two diastereoisomers. They were separated by a preparative TLC to give approximately equal quantities of the two isomers (R_f=0.36 and 0.56 on silica in hexane-ethylacetate (2 : 1). The slower-running (more polar) isomer was obtained by crystallising from ethanol, mp 116-119°C. The faster-running (less polar) isomer was obtained by crystallising from ethanol; *cis/trans* mixture mp 85~86°C (lit. European patent 175,466 (1985));

The slower-running (more polar) isomer (*cis*); mp 116~119°C; IR (KBr) 3390, 1670, 1605, 1240 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 2.05 (m, 2 H) 2.25 (m, 1

H), 2.8-3.1 (m, 2 H), 3.80 (s, 3 H), 4.5-4.97 (m, 1 H), 6.63-7.89 (m, 12 H)

The faster-running (less polar) isomer (*trans*); mp 92~95°C; IR (KBr) 3390, 1670, 1605, 1240 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 2.12-2.05 (m, 3 H), 2.8-3.2 (m, 2 H), 3.80 (s, 3 H), 4.55-4.88 (m, 1 H), 6.50-7.90 (m, 12 H)

cis-(9a) and *trans*-(9b) 4-Hydroxy-3-[1,2,3,4-tetrahydro-3-(4-hydroxyphenyl)-1-naphthyl]coumarin.

The *cis*-coumarin derivative **8a** (2.0 g, 5.0 mmol), acetic acid (5.0 ml) and hydrobromic acid (47%, 3.9 ml) were refluxed for 6 h and then cooled to RT. The mixture was made alkaline with 10% NaOH solution. This solution was washed with dichloromethane to remove unreacted material and then acidified. The reaction mixture was subjected to extractive workup with dichloromethane (three times) to afford the crude product. Chromatography of the crude product on silica gel (1 : 8 ethylacetate/hexane) gave the *cis*-isomer **9a** (1.8 g, 93%). Similarly, the *trans*-coumarin derivative **8b** (2.0 g, 5.0 mmol) was converted into the *trans*-isomer **9b** (1.79 g, 92.8%)

The slower-running (more polar) isomer (*cis*); IR (KBr) 3400, 1690, 1235 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 1.92-2.4 (m, 2 H) 2.45-2.55 (m, 1 H), 2.8-3.1 (m, 2 H), 4.05-4.8 (m, 2 H), 6.55-7.98 (m, 12 H).

The faster-running (less polar) isomer (*trans*); IR (KBr) 3400, 1690, 1235 cm⁻¹; ¹H NMR (CDCl₃, 80 MHz) δ 1.92-2.3 (m, 2 H) 2.45-2.60 (m, 1 H), 2.8-3.1 (m, 2 H), 4.03-4.8 (m, 2 H), 6.50-8.00 (m, 12 H)

cis-(1a) and *trans*-(1b) 4-Hydroxy-3-[1,2,3,4-tetrahydro-3-[4-(4-trifluoromethylbenzyloxy)phenyl]-1-naphthyl] coumarin.

To anhydrous *tert*-butanol (3 ml) was added clean potassium metal (180 mg, 5 mmol) under nitrogen atmosphere. The mixture was stirred until the potassium metal has reacted. To this solution was added *cis*-coumarin derivative **9a** (1.29 g, 3.4 mmol) in *tert*-butanol (10 ml). After the resulting mixture was stirred at RT for 30 min., the solvent was removed under reduced pressure at 70°C to give a solid. The solid was dissolved in DMF (10 ml) and treated with 4-trifluoromethylbenzyl bromide (0.8 g, 3.4 mmol). After stirred for 16 h at RT, it was diluted with water (50 ml). The reaction mixture was subjected to extractive workup with ether (50 ml × 3). The combined extracts were washed with brine, dried over MgSO₄ and concentrated at reduced pressure to give the crude product. Chromatography of the crude product on silica gel (1 : 3 ethyl acetate/hexane) gave *cis*-isomer **1a** (954 mg, 52.4%). Similarly, the *trans*-coumarin derivative **9b** (384 mg) was converted into the *trans*-isomer **1b** (282 mg, 52%).

The slower-running (more polar) isomer (*cis*); mp 183~184°C, R_f :0.11 [EtOAc:Hex (1:3)]; IR (KBr) 3225, 1665, 1615, 1505, 1320, 1110, 1015 cm^{-1} ; ^1H NMR (CDCl_3 , 80 MHz) δ 1.26 (m, 2 H), 2.44 (dd, $J=4$ Hz, 9.3 Hz, 1 H), 3.08 (m, 2 H), 4.85 (dd, $J=6$ Hz, 12 Hz, 1 H), 5.09 (d, $J=6$ Hz, 2H), 6.95 (m, 2 H), 7.1-7.4 (m, 8 H), 7.48-7.67 (m, 6 H); MS m/z (%): 542 (m^+ , 5.6), 381 (5.9), 290 (46.2), 222 (21.3), 163 (20.2), 159 (100), 128 (23.1), 121 (32.2), 109 (25.1)

The faster-running (less polar) isomer (*trans*); mp 153~155°C, R_f :0.20 [EtOAc:Hex (1:3)]; IR (KBr) 3225, 1665, 1615, 1505, 1320, 1110, 1015 cm^{-1} ; ^1H NMR (CDCl_3 , 80 MHz) δ 1.26 (m, 2 H), 2.33 (br s, 1 H), 3.04 (m, 2 H), 4.72 (br s, 1 H), 5.10 (s, 2 H), 6.92 (m, 2 H), 7.1-7.4 (m, 8 H), 7.5-7.75 (m, 6 H); MS m/z (%) 542 (m^+ , 5.6), 381 (5.9), 290 (46.2), 222 (21.3), 163 (20.2), 159 (100), 128 (23.1), 121 (32.2), 109 (25.1)

RESULTS AND DISCUSSION

1-(4-Methoxyphenyl)-2-phenyl-1-ethanone (**2**) was readily prepared by treatment of anisole with phenylacetyl chloride under Friedel-Crafts condition. Compound **2** underwent a Reformatsky reaction with ethyl bromoacetate to afford ethyl 3-hydroxy-3-(4-methoxyphenyl)-4-phenylbutanoate (**3**) in 97% yield. The dehydroxylation of compound **3**, employing the procedure described by Carey (Carey and Tremper 1971) provided ethyl 3-(4-methoxyphenyl)-4-phenylbutyrate (**4**), which was hydrolyzed to give 3-(4-methoxyphenyl)-4-phenylbutanoic acid (**5**). Heating acid **5** with polyphosphoric acid gave ketone **6**. Although this cyclization could give rise to either 3-(4-methoxyphenyl)-3,4-dihydronaphthalen-1(2H)-one or 3-(4-methoxybenzyl)-indan-1-one, it has been shown that in reactions of this type, six-membered rings are formed in preference to five-membered rings. Also, the carbonyl stretching band in the I.R. spectrum of the product appeared at ca 1675 cm^{-1} , characteristic of 3,4-dihydronaphthalen-1(2H)-one (Lednicer and Hauser 1958) (the corresponding absorption for substituted indanones appears ca 1720 cm^{-1}).

Reduction of **6** with sodium borohydride afforded *cis*-3-(4-methoxyphenyl)-1-tetralol (**7**). The apparently exclusive formation of the *cis* isomer is somewhat surprising in this instance, since no particular steric hindrance to the approach of the reducing species from either side would be anticipated from molecular models. In 3-(4-methoxyphenyl)-1-tetralol (**7**), the alicyclic ring is assumed to be held in a half chair conformation with the 3-substituent occupying an equatorial position (Fig. 1) (Shadbolt *et al.*, 1976), based on a ^1H NMR study.

In the ^1H NMR spectrum of compound **7** (3-(4-

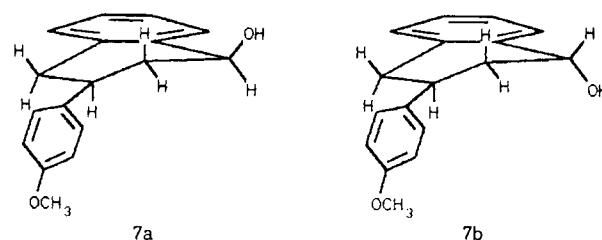


Fig. 1.

methoxyphenyl)-1-tetralol), the 1-H signal occurs as an apparent doublet of doublet centered at $\delta=4.98$ with a width of 16.27 Hz. If the 1-H is pseudo-axial, the width of the doublet of doublet will be the sum of an axial-axial and an axial-equatorial couplings, that is ca 16 Hz, whereas if the 1-H is pseudo-equatorial, the width will be the sum of an equatorial-axial and an equatorial-equatorial couplings, that is ca 7 Hz (Mitsui *et al.*, 1968; Jackman and Sternhell 1969). This suggests that the 1-H in compound **7** is pseudo-axial and that the configuration is 1,3-*cis* as in **7a** in Figure 1. Moreover, it has been suggested that reduction of 3,4-dihydro-3-phenylnaphthalen-1(2H)-one by metal hydride gives *cis*-1,2,3,4-tetrahydro-3-phenyl-1-naphthol (Clark-Lewis and Nair, 1967; Mitsui *et al.*, 1968).

Treatment of compound **7** with 4-hydroxycoumarin in the presence of catalytic amount of *p*-TsOH, produced compound **8** as a ca 1:1 mixture of two components believed to be *cis* and *trans* isomers. The ratio of *cis*- to *trans*-isomers obtained here was determined by G.L.C. to be 1:1 (t_R 4.7 and 5.7 min; 20% SE-30 on shimalite W at 160°C). The two isomers were separated by a preparative TLC to give approximately equal quantities of the two isomers (R_f 0.36 and 0.56 on silica in ethylacetate:hexane (1:2)).

The ^1H NMR spectrum of the more polar isomer (**8a**, R_f 0.36) in CDCl_3 showed the 1-H signal as a doublet of doublet centered at δ 4.9. The couplings are 6 Hz and 11 Hz, hence the 1-H is axial. This isomer was therefore assigned the *cis*-configuration (cf. Figure 1). The spectrum of the less polar isomer (**8a**, R_f 0.56) in CDCl_3 showed the 1-H signal as a triplet centered at 4.73 with coupling constant of ca 4 Hz. This indicates that the 1-H is equatorial and hence the isomer has the *trans*-configuration (cf. Fig. 1).

The major by-product from the reaction of 3-(4-methoxyphenyl)-1-tetralol (**7**) with 4-hydroxycoumarin in the presence of catalytic amount of *p*-TsOH, was isolated and identified as 2-(4-methoxyphenyl)-1,2-dihydronaphthalene, resulting from dehydration.

The compound **8a** and **8b** were demethylated with HBr in acetic acid to afford the corresponding ph-

enols **9a** and **9b**, respectively. The compound **9a** and **9b** were treated with potassium *tert*-butoxide in *tert*-butanol, and the resulting phenoxides were reacted with 4-trifluoromethylbenzyl bromide, to afford the final product **1a** and **1b**, respectively.

ACKNOWLEDGEMENTS

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